A DOENÇA PULMONAR OBSTRUTIVA CRÓNICA E O EXERCÍCIO: IMPACTO DA DOENÇA NO DECLÍNIO FUNCIONAL E IMPORTÂNCIA DO TREINO DE EXERCÍCIO NOS BENEFÍCIOS PARA A SAÚDE

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De acordo com o nº 2 do Artigo 8º do Decreto-Lei nº 388/70, a autora declara que participou na conceção, desenho, colheita de dados, interpretação de resultados e redação dos seguintes artigos originais, publicados ou submetidos a publicação e que fazem parte desta tese:

- **Estudo 1**

Bárbara C, **Rodrigues F**, Dias H, Cardoso J, Almeida J, Matos MJ, Simão P, Moutinho dos Santos J, Reis Ferreira J, Gaspar M, Gnatiuc L, Burney P. Chronic Obstructive Pulmonary Disease Prevalence in Lisbon, Portugal: The Burden of Obstructive Lung Disease Study. Rev Port Pneumol 2013;19(3):96-105. DOI: 10.1016/ j.rppneu.2012.11.004.

- **Estudo 2**

Saraiva C, Tavares Abreu T, Neves D, **Rodrigues F**. Mortality predictive factors in subjects with COPD after a pulmonary rehabilitation program – a 3 years' study. Submetido à Respiratory Care em 15 de agosto de 2015 (ID: RC-04477).

- **Estudo 3**

Rodrigues F, Matias I, Oliveira J, Vacas S, Botelho A. COPD: On Evaluating the Risk for Functional Decline. In Springer International Publishing Switzerland 2015. C.P. Kitsos et al. (Eds.), Theory and Practice of Risk Assessment, Springer Proceedings in Mathematics & Statistics 136, DOI 10.1007/978-3-319-18029-8_11.

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Rodrigues F, Papoila AL, Ligeiro D, Marques Gomes MJ, Trindade H. Acute exercise amplifies inflammation in obese patients with COPD – a prospective cohort study. Submetido à Revista Portuguesa de Pneumologia em 16 de outubro de 2015 (ID: RPP-D-15-00149).

- **Estudo 5**

Alfarroba S, **Rodrigues F**, Santos AF, Morais L. Pulmonary Rehabilitation in COPD according to GOLD categories A, B, C and D – a prospective cohort study. Submetido à Respiratory Care em 11 de julho de 2015 (ID: RC-04414).

- **Estudo 6**

Carreiro A, Santos J, **Rodrigues F**. Impact of comorbidities in pulmonary rehabilitation outcomes in patients with chronic obstructive pulmonary disease. Rev Port Pneumol 2013;19(3):106-113. DOI: 10.1016/j.rppneu.2012.12.004.

- **Estudo 7**

Santos C, **Rodrigues F**, Santos J, Morais L, Bárbara C. Pulmonary rehabilitation in COPD: effect of two aerobic exercise intensities on subject-centered outcomes - A randomized controlled trial. Respir Care 2015;60(11):1603-1609. DOI: 10.4187/ respcare.03663.

- **Estudo 8**

Barriga S, **Rodrigues F**, Bárbara C. Factors that influence physical activity in the daily life of male patients with chronic obstructive pulmonary disease. Rev Port Pneumol 2014;20(3):131-137. DOI: 10.1016/j.rppneu.2013.09.004.

- **Estudo 9**

Areias V, Ferreira D, Martins A, Matias I, Negrinho F, **Rodrigues F.** Evolution of functional capacity and health status two years after a pulmonary rehabilitation program. Rev Port Pneumol 2012;18(5):217-225. DOI: 10.1016/j.rppneu.2012.02.010.

- **Estudo 10**

Faria I, Gaspar C, Zamith M, Matias I, César das Neves R, **Rodrigues F**, Bárbara C. TELEMOLD Project: Oximetry and Exercise Telemonitoring to Improve Long-Term Oxygen Therapy. TELEMEDICINE and e-HEALTH 2014; 20 (7): 1-7, DOI: 10.1089/tmj.2013.0248.

Foram igualmente incluídos na estrutura teórica da tese, excertos de outros trabalhos publicados ou submetidos a publicação:

Rodrigues F. Estudo dos fatores limitativos do exercício físico em doentes com DPOC. Rev Port Pneumol 2004,X(1):9-61. PMID: 15190427.

Reis Ferreira JM, Matos MJ, **Rodrigues F**, Belo A, Brites H, Cardoso J, Simão P, Moutinho dos Santos J, Almeida J, Gouveia A, Bárbara C. Prevalência de obstrução numa população exposta ao fumo do tabaco - PROJETO PNEUMOBIL. Rev Port Pneumol 2009; XV(5):803-46. PMID: 19649542.

Rodrigues F. Importância de fatores extrapulmonares – depressão, fraqueza muscular, qualidade de vida – na evolução da DPOC. Rev Port Pneumol 2010, 6:709-715. PMID: 20945588.

Cardoso J, Reis Ferreira JM, Almeida J, Moutinho Santos J, **Rodrigues F**, Matos MJ. Doença Pulmonar Obstrutiva Crónica em PORTUGAL: estudo Pneumobil (1995) e estudo de prevalência revisitados. Rev Port Pneumol 2013:19(3):88-95. DOI: 10.1016/ j.rppneu.2012.11.005.

Rodrigues F, Grafino M, Papoila AL, Faria I, Pontes de Mata J, Félix F. Avaliação do risco cirúrgico na neoplasia do pulmão em doentes com DPOC. Submetido a publicação à Revista Portuguesa de Pneumologia em 4 dezembro de 2015 (ID: RPP-D-15-00180).

Almeida P, **Rodrigues F**. Exercise training modalities and strategies to improve exercise performance in patients with respiratory disease. Rev Port Pneumol 2014;20(1):36-41. DOI: 10.1016/j.rppneu.2013.10.004.

ÍNDICE

Lista de abreviaturas

6MWD	*6-minute walking distance*
6MWT	*6-minute walking test*
ACCP	*American College of Chest Physicians*
ADL	*Activities of Daily Living*
ATS	*American Thoracic Society*
BDI/TDI	*Mahler's Basal / Transitional Dyspnea Index*
BMI	*Body Mass Index*
BODE	*Body Mass Index, Obstruction, Dyspnea, Exercise*
BOLD	*Burden of Obstructive Lung Disease*
BTS	*British Thoracic Society*
COPD	*Chronic Obstructive Pulmonary Disease*
CAT	*COPD Assessment Test*
CLET	*Constant-Load Exercise Test*
COTE	*COPD specific comorbidity test*
CRP	*C-reactive protein*
Ct	*Threshold cycle*
CWR	*Constant work rate endurance test*
DALYs	*Disability-Adjusted Life Years*
DCt	*Delta delta Ct*
DLCO	*Diffusing capacity for carbon monoxide*
DLCO/VA	*Carbon monoxide transfer coefficient*
DPOC	Doença Pulmonar Obstrutiva Crónica
ERS	*European Respiratory Society*
FEV_1	*Forced expiratory volume in the first second*
FEV_1/FVC	*Forced expiratory volume in the first second / Forced vital capacity ratio*
FVC	*Forced vital capacity*
GOLD	*Global Initiative for Obstructive Lung Diseases*
HADS	*Hospital Anxiety and Depression scale*
HRQOL	*Health-Related Quality of Life*
IET	*Incremental Exercise Test*
IFNg ou IFNγ	*Interferon gamma*

IL-1b ou IL-1β	*Interleukin 1 beta*
IL-6	*Interleukin 6*
IL-8	*Interleukin 8*
IMPALA	*Impact on Life Activities*
iNOS ou NOS2A	*Inducible nitric oxide synthase*
KCO	*Carbon monoxide transfer coefficient*
LCADL	*London Chest Activity of Daily Living Scale*
LTOT	*Long-term oxygen therapy*
MCID	*Minimal clinical important difference*
MET	*Metabolic equivalent of task*
mMRC	*Modified Medical Research Council*
mRNA	*Messenger ribonucleic acid*
NHANES	*National Health and Nutrition Examination Survey*
OLD	Oxigenoterapia de longa duração
$PaCO_2$	*Arterial partial pressure of carbon dioxide*
PaO_2	*Arterial partial pressure of oxygen*
PCR	*Polymerase Chain Reaction*
peakWR	*Peak work rate*
PR	*Pulmonary Rehabilitation*
PRP	*Pulmonary Rehabilitation Program*
RDD	*Random-Digit-Dialling*
RM	*Maximum Repetition*
RR	Reabilitação Respiratória
RT-PCR	*Reverse transcriptase polymerase chain reaction*
RV	*Residual Volume*
SGRQ	*Saint George's Respiratory Questionnaire*
TelemOLD	Telemonitorização da oxigenoterapia de longa duração
TGFb1 ou TGFβ1	*Transforming growth factor beta1*
TLC	*Total Lung Capacity*
TNFa ou TNFα	*Tumour necrosis factor alpha*
UMA	Unidades-maço ano
Wmax	Potência aeróbica máxima

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Resumo

A reabilitação respiratória (RR) é uma intervenção abrangente e interdisciplinar dirigida aos doentes respiratórios crónicos e inclui o treino de exercício, programas de educação e de modificação comportamental, entre outros, desenhados individualmente para melhorar o desempenho físico e psicossocial e promover a adesão a longo prazo a comportamentos promotores de saúde. A doença pulmonar obstrutiva crónica (DPOC) é uma doença comum, afetando cerca de 210 milhões de pessoas em todo o mundo, com elevada mortalidade e com custos económicos significativos decorrentes do agravamento progressivo da doença, das hospitalizações e de reinternamentos frequentes.

Apesar do crescente conhecimento da DPOC e do papel da RR nos benefícios para a saúde, existem aspetos ainda não esclarecidos que têm impacto na prática clínica e de investigação e nas decisões das autoridades de saúde.

A primeira parte desta tese focou a DPOC e o seu impacto negativo e incluiu: o estudo da prevalência da DPOC em Portugal; os fatores clínicos e funcionais que se associam à mortalidade em doentes com DPOC avançada; a morbilidade, impacto funcional e risco dos doentes se tornarem dependentes para as atividades diárias e a influência da inflamação sistémica.

A prevalência estimada da DPOC de 14,2% indica que esta é uma doença comum em Portugal e alerta para a necessidade de uma maior sensibilização da população, dos profissionais de saúde e autoridades de saúde com vista a um diagnóstico precoce e à alocação dos recursos terapêuticos adequados.

A elevada taxa de mortalidade em doentes com DPOC avançada - 36,6% em 3 anos - associou-se a insuficiência respiratória, a elevado número de exacerbações, ao cancro do pulmão e a reduzida capacidade funcional para a marcha, salientando a importância da referenciação precoce para RR, a identificação e o tratamento das comorbilidades e a prevenção das exacerbações.

A aplicação de um questionário que avaliou as atividades da vida diária básicas e instrumentais, permitiu identificar um marcador clínico do risco de dependência, complementando as avaliações funcionais e associando-se a outros marcadores de mau prognóstico, como as exacerbações.

Em doentes com DPOC, com FEV_1 médio de 46,76% (desvio padrão: 20,90%), 67% da categoria D do GOLD, verificou-se uma associação positiva entre a expressão de genes inflamatórios avaliada pela reação em cadeia da polimerase (ARN mensageiro de IFNg, IL1b, IL6, IL8, TNFa, TGFb1, iNOS) e o índice de massa corporal em repouso, acentuando-se após o exercício. Este estudo aponta a inflamação como o potencial elo de ligação entre a obesidade e a inflamação sistémica em doentes com DPOC.

A segunda parte da tese focou a RR, nomeadamente os seus efeitos em doentes das categorias GOLD A, B, C e D; o impacto das comorbilidades nos resultados da RR e os resultados de diferentes intensidades de treino aeróbio.

Após o programa de RR, verificaram-se melhorias significativas na capacidade de exercício funcional e de *endurance* e no estado geral de saúde dos doentes de todas as categorias GOLD. Esta classificação não distingue os doentes que melhor poderão beneficiar desta intervenção, indicando que devem ser referenciados para RR, os doentes sintomáticos ou com repercussão na qualidade de vida, independentemente da categoria da DPOC a que pertençam.

A prevalência das comorbilidades no grupo de doentes com DPOC que é referenciado para RR, é elevada, sendo as mais frequentes, as cardiovasculares, as respiratórias e as psicológicas. Apesar de poderem diminuir o impacto da RR, os resultados desta foram semelhantes independentemente do número de comorbilidades. A identificação e o tratamento sistemáticos das comorbilidades conferem maior segurança clínica a esta intervenção terapêutica a qual, por apresentar bons resultados, não deve limitar a referenciação dos doentes.

Com o programa de RR, verificou-se melhoria significativa em todos os resultados centrados no doente para ambas as intensidades de treino aeróbio, a 60% e a 80% da potência aeróbica máxima (Wmax), com melhoria do estado geral de saúde, nos sintomas e na capacidade para o exercício, o que questiona a indicação sistemática de elevadas intensidades de treino em doentes com DPOC para a obtenção de benefícios a curto prazo.

Na terceira e última parte da tese foi estudado o papel da atividade física na DPOC, focando os fatores que influenciam a atividade física diária; a evolução da capacidade funcional e o estado de saúde 2 anos após um programa de RR e o papel da telemonitorização na quantificação e monitorização da atividade física.

Confirmámos que os doentes com DPOC são marcadamente sedentários e os fatores que se associaram ao sedentarismo nestes doentes foram a dispneia e a distância percorrida na prova de marcha de seis minutos. Este estudo sublinha a importância do controlo sintomático, nomeadamente da dispneia, bem como, mais uma vez, o potencial papel da reabilitação respiratória no aumento da capacidade funcional para o exercício e na aquisição de hábitos de vida fisicamente ativa.

Verificámos que, apesar de os doentes com DPOC apresentarem benefícios clinicamente significativos na capacidade funcional para o exercício e no estado geral de saúde com o programa de RR, apenas os que se mantêm ativos, podem, no final dos dois anos de seguimento, manter os efeitos benéficos desse programa.

O sistema de telemonitorização que combina a oximetria e a quantificação da atividade física provou ser clinicamente útil na avaliação da necessidade de oxigenoterapia de longa duração (OLD) e na aferição do débito de oxigénio em repouso, no esforço e no

sono, podendo contribuir para uma melhor adequação da prescrição da OLD. A monitorização dos níveis de atividade física regular é um importante instrumento de avaliação dos programas de RR e o seu uso potencial na telereabilitação permitirá prolongar a eficácia dos programas e reduzir os custos associados aos cuidados de saúde.

Abstract

Pulmonary rehabilitation (PR) is a comprehensive interdisciplinary intervention that includes, but is not limited to, exercise training, education, and behavior change, individually designed to improve physical and psychological conditions of people with chronic respiratory disease and to promote long-term adherence to health-enhancing behaviors.

Chronic obstructive pulmonary disease (COPD) is a common disease, affecting about 210 million people worldwide, with high mortality and significant health-related costs due to disease progression, hospitalizations and frequent hospital readmissions.

Although the increasing knowledge about COPD and benefitial outcomes of PR, some aspects with impact in clinical practice, research and health authorities' decisions, remain to be clarified.

The first part of this thesis focused on COPD and its negative impact, including the study of COPD prevalence in Portugal; clinical and functional factors associated with mortality in advanced COPD patients; morbidity, functional impact and risk of others' dependance to perform activities of daily living; and the role of systemic inflammation.

The evidence of 14.2% estimated COPD prevalence as a common disease in Portugal raises the need of an increasing awareness of population, health care professionals and health authorities towards an earlier diagnosis and apropriate treatment resources allocation.

High mortality in patients with advanced COPD – 36.6% in 3 years - was associated with respiratory failure, high frequency of exacerbations, lung cancer and a low functional capacity in walking. This highlightens the importance of an earlier referral to PR, comorbidity identification and treatment, and prevention of exacerbations.

A questionnaire evaluated basic and instrumental activities of daily living, and identified a clinical marker of the risk of becoming dependent. This clinical marker complemented other functional evaluations and was associated with prognosis markers such as the number of exacerbations.

In COPD patients with a mean FEV_1 46.76% (SD 20.90%), 67% belonging to GOLD grade D, we found a positive association between inflammatory gene expression evaluated by polymerase chain reaction (IFNg, IL1b, IL6, IL8, TNFa, TGFb1, iNOS RNA messenger) and body mass index at rest, and a further increase with exercise. This study evidenced obesity as one potential link between COPD and systemic inflammation.

The second part of this thesis focused PR, namely its outcomes in patients of GOLD categories A, B, C and D; comorbidities impact in PR outcomes, and the impact of different exercise training intensities in patient related outcomes.

With PR intervention, we found significant improvement in functional exercise capacity, endurance exercise capacity and health status in patients of all GOLD categories. This classification did not differentiate which patients would benefit more from PR, hence all symptomatic patients with a negative impact in health status should be referred to PR, regardless of the GOLD category they belong to.

There is a high prevalence of comorbidities in COPD patients referred to PR, being cardiovascular, respiratory and psychological, the most prevalent. Although some comorbidities might reduce PR impact, the results were similar regardless of the number of comorbidities. Systematic comorbidities identification and treatment provides safety to PR intervention, and its good results should not preclude patients referral.

With PR intervention we found a significant improvement in all patient reported outcomes for exercise training intensities at 60% and 80% maximum work rate (Wmax), namely in health status, symptoms and exercise capacity. These findings challenge the current systematic indication of high exercise training intensities to achieve PR short-term benefits.

In the third and last part of the thesis, the role of physical activity in COPD was studied, focusing factors that may influence daily physical activity; the evolution of functional capacity and health status two years after a PR program, and the role of a telemonitoring system in physical activity quantification and monitoring.

We confirmed that COPD patients are markedly inactive and factors associated with a sedentary lifestyle are dyspnea and 6 minute walking distance. This study emphasized the importance of symptom control, namely of dyspnea, as well as, once again, the potential role of PR in functional exercise improvement and in integrating physically active habits in daily life.

We verified that, although COPD patients improve functional exercise capacity and health status after a PR program, only those who kept physical activity habits were able to maintain those effects after 2 years of follow-up.

A telemonitoring system that combines oximetry and physical activity quantification proved to be clinically useful in the evaluation of long-term oxygen therapy (LTOT) indication, as well as in the titration of oxygen levels at rest, exertion, and sleeping, which might contribute to a more adequate LTOT prescription.

Monitoring of daily physical activity levels is an important PR evaluation instrument and its potential use in telerehabilitation might allow lengthening programs efficacy, while reducing health-care costs.

Estrutura da Tese

A presente tese está organizada em cinco capítulos.

No Capítulo 1 é feita uma introdução geral ao tema da reabilitação respiratória em doentes com DPOC, incluindo uma revisão da literatura que contribuiu para o estado da arte sobre este tema. Segue-se uma introdução teórica aos trabalhos que foram desenvolvidos na tese: prevalência, mortalidade e morbilidade da DPOC; papel da inflamação sistémica; programas de reabilitação respiratória: candidatos, impacto das comorbilidades nos resultados e o efeito das intensidades de treino; importância da atividade física regular: fatores que a influenciam, manutenção da atividade física após os programas e sistema de telemonitorização da atividade física.

No Capítulo 2 são enunciados os principais objetivos de cada um dos trabalhos que foram desenvolvidos.

No Capítulo 3 é apresentada sumariamente a metodologia de cada um dos trabalhos, sendo esta mais detalhada nos respetivos artigos.

O Capítulo 4 inclui os sete estudos publicados e os três submetidos a publicação, agrupados em três seções: a DPOC (estudos 1 a 4), os programas de reabilitação respiratória em doentes com DPOC (estudos 5 a 7) e a importância da atividade física na DPOC (estudos 8 a 10).

No Capítulo 5 é apresentada uma discussão sumária com as principais conclusões dos estudos e algumas perspetivas para linhas de investigação futuras.

Prefácio

A reabilitação tem por objetivo restaurar em cada indivíduo o seu máximo potencial físico, mental, emocional, social e vocacional, de que ele ou ela é capaz [1].

Conselho de Reabilitação, 1942

O meu primeiro contacto com a reabilitação surgiu, aos 18 anos, como trabalhadora-estudante, na Clínica de Medicina Física e de Reabilitação, dirigida pela Dr.ª Hermínia Grenha.

Já como interna do internato complementar de Pneumologia, foi durante o estágio na Unidade de Readaptação Funcional Respiratória do Hospital Pulido Valente em 1993, com a Dr.ª Camila Canteiro, que compreendi o alcance desta terapêutica na melhoria do estado de saúde dos doentes com patologia respiratória.

O estágio de fisiopatologia respiratória que realizei em 1994 na Clínica Mayo com os Drs. Robert E. Hyatt e Paul Scanlon, em Rochester, EUA, e os cursos sobre a prova de exercício cardiopulmonar que fiz com os professores Karlman Wasserman, James Hansen, Brian Whipp e Paolo Palange em Berlim (2000), no Porto (2008) e em Roma 2010) aprofundaram os meus conhecimentos sobre as alterações da função respiratória em repouso e no esforço. Na sequência do estudo destas matérias, desenvolvi um trabalho de investigação sobre a fisiopatologia do exercício no doente com DPOC que culminou, em 2002, com a Tese de Mestrado sobre o tema "Hiperinsuflação pulmonar como fator limitativo do exercício físico em doentes com DPOC", tendo como orientador, o Professor Doutor Ramiro Ávila.

A experiência adquirida desde 2007 com o trabalho desenvolvido como pneumologista dedicada à reabilitação respiratória e a atualização nesta área, com a frequência dos cursos de reabilitação respiratória realizados em 2012, no Centro de Reabilitação do Hospital de Leuven, Bélgica (*Faculty of Kinesiology and Rehabilitation Sciences*, Universidade de Leuven) e em 2014 no CIRO (*Centre of expertise for chronic organ failure*, Universidade de Maastricht) em Horn, Holanda, ocorreram a par do desenvolvimento dos trabalhos que deram origem a esta Tese.

Optei por estudar a reabilitação na doença pulmonar obstrutiva crónica, por se tratar de uma doença que, embora subestimada durante muitos anos, tem vindo a revelar um enorme impacto na qualidade de vida, nos custos associados e na esperança de vida dos seus portadores. Esse é o motivo pelo qual se tornou alvo de intensa investigação, nomeadamente em estudos que envolvem a reabilitação, cujo papel nos benefícios para a saúde é hoje inquestionável.

A prática clínica e o estudo dos trabalhos publicados sobre reabilitação respiratória em doentes com DPOC, tornaram evidentes aspetos ainda não esclarecidos sobre esta área terapêutica e sobre a DPOC. Estas foram as interrogações que mais desafios me colocaram no dia-a-dia. Tendo em conta que as respostas a estas questões poderão contribuir para otimizar o conhecimento e os resultados atingidos na praxis médica, procurei investigá-las, mediante a realização de estudos científicos.

1

INTRODUÇÃO

Capítulo 1

A reabilitação respiratória

Nota histórica

Remontam aos primórdios da Medicina, as primeiras referências ao exercício físico como benéfico para a saúde. Galeno de Pérgamo (129-199 dC), um dos médicos mais influentes de todos os tempos, produziu pelo menos 80 tratados sobre inúmeros tópicos, incluindo os efeitos benéficos do exercício e as consequências deletérias do sedentarismo. Ensinou as "leis da saúde", ainda hoje tão atuais: "respirar ar puro, comer alimentos apropriados, beber as bebidas certas, exercitar-se, dormir por um período suficiente, defecar uma vez ao dia e controlar as emoções" [2].

Transitando para a era contemporânea, em 1895, o Dr. Charles Denison, Professor de Doenças do Tórax e Climatologia na Universidade de Denver, foi o primeiro a afirmar que as caminhadas diárias, a higiene e a dieta alimentar são importantes para que os doentes respiratórios incapacitados possam obter relaxamento mental, bem-estar e prosperidade [3].

A reabilitação respiratória (RR) inicia os primeiros passos em meados do século passado, a par do reconhecimento do impacto negativo da DPOC e do advento da oxigenoterapia. Alvan Barach publica em 1926, a descrição da tenda de oxigénio para redução da dispneia em doentes críticos com pneumonia [4], em 1936 descreve o uso do heliox para alívio da dispneia em doentes com asma e enfisema [5], nos anos 50 desenvolve sistemas portáteis de oxigenoterapia para doentes com enfisema [6] e é o próprio que descreve em 1952, os benefícios do exercício terapêutico em dois doentes com enfisema e dispneia de esforço, com melhoria evidente na capacidade para o exercício, sugerindo uma resposta fisiológica similar à obtida com os programas de treino em atletas [7].

Thomas Petty, eminente pneumologista, foi o criador do primeiro programa multidisciplinar de reabilitação respiratória nos anos 60. Este incluía instruções individualizadas sobre a doença, técnicas de higiene brônquica, exercícios respiratórios, recondicionamento físico, otimização farmacológica individualizada e, tendo estabelecido as bases científicas da oxigenoterapia, introduziu a administração de oxigénio suplementar [8]. Em 1969 publicou no artigo "Um programa de cuidados abrangentes para indivíduos com obstrução crónica das vias aéreas" os primeiros resultados da eficácia a curto e a longo prazo dos programas de reabilitação respiratória, com melhoria na tolerância ao exercício, redução das hospitalizações e retorno à atividade profissional [9]. Este artigo foi um marco na história da reabilitação de portadores de doença respiratória crónica.

Em 1974 é apresentada no Congresso anual da *American College of Chest Physicians* a primeira definição de reabilitação respiratória [10] e em 1981 a *American Thoracic Society* publica uma recomendação oficial com os componentes da RR e os seus benefícios, definindo o exercício terapêutico como um componente essencial [11].

Em 1974 foram desenvolvidas as primeiras provas de marcha e em 1987, o primeiro questionário de qualidade de vida relacionada com a saúde (*Chronic Respiratory Questionnaire*) [12] e Mahler em 1988, elabora o 1º questionário de dispneia [13].

A evidência científica crescente deu fundamento ao papel essencial da reabilitação respiratória. Em 1991, Casaburi e colaboradores demonstram que o treino de exercício tem um efeito fisiológico dose-dependente [14].

O primeiro documento publicado a nível internacional com uma forte recomendação sobre o papel da reabilitação respiratória no tratamento dos doentes com DPOC foi publicado em 1992 [15]. Em 1994, Reardon e colaboradores demonstram melhoria da dispneia de esforço após os programas de reabilitação respiratória [16] e, no mesmo ano, Goldstein e colaboradores demonstram a melhoria na qualidade de vida [17]. Em 1995, Ries e colaboradores evidenciam a melhoria na tolerância ao exercício, nos sintomas e na autoeficácia na marcha [18]. Maltais e colaboradores demonstram em 1996, que a DPOC também é uma doença dos músculos e por isso, melhora com o exercício terapêutico [19]. Em 2000 e 2001, Griffiths e colaboradores evidenciam ganhos em saúde para além da

capacidade de exercício e da qualidade de vida, demonstrando a redução subsequente da utilização dos recursos de saúde, como os internamentos e as consultas [20, 21].

A evolução dos conhecimentos e a evidência científica do papel da reabilitação respiratória devem igualmente a nomes como Guyatt, Goldstein, ZuWallack, Rochester, Nici, Make, Lacasse, Decramer, Wouters, Morgan, Donner, Schols, Singh, Gosselink, Spruit, Aymerich, Troosters, Vogiatzis, Clini, Holland, Puhan, Garrod e Pitta, entre outros, os inúmeros trabalhos publicados. O conjunto de evidências científicas foi reunido e publicado sob a forma de recomendações pelas sociedades científicas internacionais - *American Thoracic Society, European Respiratory Society, British Thoracic Society, American Association for Cardiovascular and Pulmonary Rehabilitation, American Association for Respiratory Care, American College of Chest Physicians*[22-25].

Em 2001 o projeto GOLD (*Global Initiative for Chronic Obstructive Lung Disease*) indica a reabilitação respiratória como terapêutica padrão da DPOC e, em 2008, coloca-a no algoritmo do tratamento da DPOC estável [26].

Em Portugal, a implementação da Reabilitação foi iniciada no Porto, pelo Dr. Alberto Leal e em Lisboa pela Dr.ª Camila Canteiro. Tendo estagiado em 1961 com o Dr. Alberto Leal, a Dr.ª Camila Canteiro, incentivada pelo seu Diretor do Serviço no Hospital de Santa Maria e mentor, Professor Doutor Thomé Villar, aprofundou os conceitos e práticas da reabilitação com Thomas Petty (Denver, EUA), Levi-Valensi (Amiens, França), Carat (Nancy, França), Sadoul (França), Hertzog (Basel, Suíça), Macagno (Itália), entre outros, e implementou, ainda na década de 60, o Serviço de Readaptação Funcional Respiratória no Hospital de Pulido Valente e no Hospital de Santa Maria. Foi ainda pioneira em Portugal, na criação das consultas de Oxigenoterapia de Longa Duração (em 1987) e de Tabagismo (em 1988), do primeiro programa de apoio domiciliário ao doente insuficiente respiratório (em 1998) e da primeira enfermaria de ventilação eletiva (1999).

Atualmente existem a nível dos hospitais públicos, 24 unidades de reabilitação respiratória com equipas multidisciplinares, das quais, 20 estão equipadas para oferecer programas de treino de exercício, componente basilar da reabilitação respiratória [27]. Contudo, à semelhança do que acontece em outros países, em que o acesso aos

programas de reabilitação é ainda muito pequeno - 1% da população com DPOC no Reino Unido [28], menos do que 1% dos doentes com DPOC moderada a grave na Austrália [29] ou 0,2% dos doentes com DPOC na Suécia [30] - estima-se que existe um número muito baixo de doentes com DPOC integrados em programas de reabilitação respiratória nos hospitais do Serviço Nacional de Saúde português - 0,05% [31]. Estes dados evidenciam a necessidade de envidar estratégias para alterar esta realidade, podendo passar por uma maior divulgação dos programas de reabilitação e dos seus benefícios junto da população de doentes, dos profissionais de saúde e das autoridades de saúde, alargar a oferta de programas a outra áreas da saúde, nomeadamente aos Cuidados de Saúde Primários, tal como já ocorre na Holanda [32] e aumentar a capacidade de resposta das unidades já existentes.

Em 2005 é publicado o Programa Nacional de Prevenção e Controlo da DPOC, no qual "devem ser, progressivamente, criadas condições de alargamento da acessibilidade do doente com DPOC a cuidados de reabilitação, segundo critérios de referenciação entre unidades de saúde, a definir no âmbito geográfico de cada Administração Regional de Saúde" [33].

Em outubro de 2009, a Direção Geral de Saúde publica a circular informativa 40A/DSPCD sob o título "Orientações Técnicas sobre Reabilitação Respiratória" [34] e, no mesmo ano, a Comissão de Trabalho de Reabilitação Respiratória da Sociedade Portuguesa de Pneumologia publica o documento de trabalho "Reabilitação Respiratória. Uma estratégia para a sua implementação" com o objetivo de incentivar os profissionais de Saúde no sentido da criação e desenvolvimento de programas de reabilitação [35].

Definição

A reabilitação respiratória foi definida pela primeira vez pelo comité da *American College of Chest Physicians* em 1974 como uma arte da prática médica em que um programa multidisciplinar desenhado individualmente e incluindo o diagnóstico preciso, a terapêutica, o suporte emocional e a educação, estabiliza ou reverte a fisiopatologia e a

psicopatologia das doenças pulmonares e procura restituir no doente a sua máxima capacidade funcional possível, atendendo à sua incapacidade e situação geral de vida [10].

A evolução do seu conceito levou à definição atual: intervenção abrangente e interdisciplinar dirigida aos doentes respiratórios crónicos, realizada por profissionais de saúde (médico, fisioterapeuta, psicólogo, enfermeiro, nutricionista, entre outros). Baseia-se numa avaliação rigorosa, que permite elaborar um programa de reabilitação individualizado e inclui o treino de exercício, programas de educação e de modificação comportamental, entre outros, desenhados para melhorar a condição física e psicossocial e promover a adesão a longo prazo a comportamentos promotores de saúde [23]. A nova definição enfatiza o carácter holístico e interdisciplinar da intervenção e coloca a RR no âmbito dos cuidados de saúde integrados.

Candidatos

São candidatos aos programas de RR, os doentes com patologia respiratória crónica cujos sintomas (dispneia, fadiga) e/ou limitações da capacidade funcional persistem, apesar da otimização da terapêutica [22, 23]; doentes com dificuldade na realização das atividades da vida diária em casa ou no seu local de trabalho, com perda de qualidade de vida atribuível à sua doença respiratória, nomeadamente com impacto psicológico ou social [23]; doentes com elevado consumo dos recursos de saúde, nomeadamente consultas e internamentos; após episódios de internamento por exacerbação grave da doença de base [36]; doentes desnutridos; doentes com dificuldade no cumprimento da terapêutica; doentes com insuficiência respiratória, para adaptação aos dispositivos de oxigenoterapia e/ou ventilação domiciliárias [37].

As evidências científicas têm demonstrado benefícios em praticamente todas as patologias respiratórias: doenças obstrutivas como a DPOC [38], a asma [39, 40], as bronquiectasias [41] ou a fibrose quística [42]; doenças de caráter restritivo, como a fibrose pulmonar [43, 44], as doenças da parede torácica [45] ou as doenças neuromusculares [46, 47]; no cancro do pulmão (pré e pós-operatório e em fase avançada da doença) [48-51], no pré e pós-operatório de cirurgia torácica ou abdominal [52, 53]; no pré e pós transplante pulmonar [54]; na hipertensão pulmonar primária [55], entre outros.

Existem poucas situações que contraindicam a referenciação para RR: a total falta de motivação e de adesão; doenças que condicionam a marcha (exemplo: artrite grave ou doença vascular periférica grave) ou quando pode agravar uma condição clínica instável (exemplo: doença cardiovascular descompensada) [56]. Um défice cognitivo significativo ou uma doença psiquiátrica podem igualmente impedir o doente de seguir as recomendações dadas no programa de RR [57].

Equipa e locais de intervenção

A equipa de RR é multidisciplinar, envolvendo vários profissionais, de acordo com as necessidades e limitações dos doentes. Incluem-se nesta equipa, o pneumologista (que habitualmente é o coordenador), fisioterapeutas, fisiologistas do exercício, enfermeiros especializados, terapeutas ocupacionais, nutricionistas, psicólogos e assistentes sociais. Podem ainda colaborar com a equipa, psiquiatras, cardiologistas, técnicos de cardiopneumologia, entre outros [24]. O carácter interdisciplinar das equipas implica uma comunicação fácil e uma colaboração ativa entre os vários profissionais, cada um conhecendo não apenas a sua área, mas também os princípios gerais da atuação dos restantes elementos da equipa [58].

Os programas de RR podem ser administrados em unidades de reabilitação localizadas nos hospitais ou em centros de reabilitação da comunidade ou ainda no domicílio do doente. Em contexto hospitalar, podem ser efetuados em regime de internamento [59] ou em ambulatório [60]. Na Áustria, todos os programas são realizados em internamento o que limita a acessibilidade e aumenta a lista de espera [61]. Na Alemanha, a RR dos doentes com fibrose pulmonar também é exclusivamente feita em internamento [62]. Em Portugal, não é prática comum internar eletivamente um doente para realizar RR. Mais frequentemente, o internamento é justificado por agudização da doença crónica (exemplo, DPOC) ou por uma patologia aguda (exemplo, pneumonia ou derrame pleural) e é neste contexto que os doentes beneficiam das técnicas de Fisioterapia, do ensino da enfermeira ou da intervenção da Psicologia Clínica, sendo posteriormente orientados para os programas de RR em ambulatório.

Em ambulatório, os programas de RR decorrem em ambiente hospitalar ou na comunidade. Por último, a RR pode ser aplicada no domicílio do doente, com a presença de técnicos, ou monitorizando à distância através da imagem (exemplo, por *Skype*), por Internet ou por telefone [63-65]. Com os recursos apropriados e em doentes estáveis, os programas de RR aplicados no domicílio e em ambiente hospitalar, têm resultados equivalentes [66-68].

A RR pode ser administrada quer em fase estável da doença, quer após exacerbação [36]. Os doentes internados podem beneficiar da RR nas enfermarias, ou mesmo em contexto de internamento nas unidades de cuidados intensivos, sendo os programas adaptados à condição clínica em cada caso [69, 70].

Objetivos e componentes dos programas

Os principais objetivos dos programas de RR são a redução de sintomas e da incapacidade, melhorar a qualidade de vida e aumentar a participação física e emocional dos doentes nas atividades diárias [71, 72].

Para atingir estes objetivos, a RR integra um conjunto de componentes com evidência consistente na literatura científica [24]. A intervenção com maior evidência científica é o treino de exercício, em particular o treino aeróbio e o treino de força muscular [38].

Outras técnicas têm apresentado um menor grau de evidência: o treino dos músculos inspiratórios não está indicado em todos os doentes, já que os melhores resultados se verificam apenas nos casos em que existe redução significativa da força destes músculos e em que os doentes referem dispneia de esforço, não tolerando o treino de exercício clássico [73, 74]. A respiração com freio labial, a anteflexão do tronco (posição de cocheiro) e a utilização de auxiliares na marcha, como o andarilho ou os bastões de apoio à marcha nórdica, reduzem o trabalho ventilatório e podem aliviar a dispneia em doentes com DPOC [73, 75, 76].

Quanto às técnicas de depuração das vias aéreas para limpeza do muco, incluindo as manobras de expiração forçada, elas podem ser aplicadas isoladamente ou em

combinação, de acordo com a eficácia documentada caso a caso e com a preferência do doente, tendo o cuidado de evitar o colapso traqueobrônquico [73]. A compressão torácica manual durante a tosse ou o *huffing* só devem ser aplicadas em doentes com fraqueza muscular associada [73]. Embora as evidências científicas na aplicação das técnicas de depuração das vias aéreas em doentes com DPOC demonstrem poucos benefícios clínicos, elas são seguras e podem ser aplicadas, quer em fase de agudização da doença, quer em fase estável [77].

Outro dos componentes importantes dos programas de RR é a educação para a autogestão da doença. Esta tem por objetivo, não apenas proporcionar ao doente a melhoria dos conhecimentos sobre a doença e o seu tratamento, mas sobretudo ajudá-lo a modificar comportamentos para a obtenção de um estilo de vida mais saudável (atividade física regular, alimentação adequada, cessação tabágica, melhor adesão à terapêutica) [24].

Incluir nos programas o ensino do reconhecimento das exacerbações e um plano de ação escrito para o seu rápido tratamento, pode reduzir o número de hospitalizações por exacerbação de DPOC [78].

Promover a autoeficácia – confiança individual em conseguir levar a cabo determinada tarefa – no decorrer dos programas de RR, pode facilitar, por exemplo, a adoção de um estilo de vida fisicamente ativo [79].

A intervenção nutricional está indicada nos doentes com alterações da composição corporal [23]. O suporte social e a integração dos cuidadores nos programas de educação para a autogestão da doença poderão beneficiar os doentes isolados ou com limitações económicas [80, 81] e melhorar as estratégias de *coping* familiar [81].

Treino de exercício

Por se tratar da componente da RR com maior evidência científica e clínica de benefícios para os doentes [38], é considerada essencial em todos os programas, pelo que são aqui desenvolvidos alguns aspetos relacionados com a fisiopatologia do exercício no doente respiratório e os benefícios e princípios do treino nestes doentes.

Os doentes com patologia respiratória podem apresentar vários tipos de limitações aquando da realização de exercícios:

- **Limitação ventilatória** – em doentes com DPOC, a obstrução brônquica e a hiperinsuflação pulmonar estática e dinâmica, têm como consequência um aumento do trabalho ventilatório e o agravamento da dispneia [82, 83].
- As **alterações das trocas gasosas**, nomeadamente, a hipoxemia, que aumenta a resposta do comando ventilatório através da estimulação dos quimiorrecetores centrais (medulares) e periféricos (corpos carotídeos e aórticos), tem como consequência a hiperventilação e um efeito direto potencial na indução da dispneia [82].
- **Fraqueza relativa dos músculos inspiratórios** – Em doentes com DPOC avançada, a força diafragmática reduz-se para cerca de 20 a 30% comparativamente aos controlos saudáveis [84]. Esta ocorre por sobrecarga devida a aumento da resistência das vias aéreas (carga resistiva), pela hiperinsuflação com desvantagem mecânica do diafragma (carga elástica) e por aumento do trabalho para contrariar a pressão positiva das vias aéreas no final da expiração (carga limiar ou *threshold*) [82, 85].
- **Disfunção dos músculos periféricos** – definida como a incapacidade no desempenho muscular resultante da perda de força, de *endurance* ou de ambas, ocorre em cerca de um terço dos doentes com patologia respiratória crónica mesmo em fases iniciais da doença [84]. Pode ser devida a vários fatores: descondicionamento devido à inatividade, inflamação sistémica, *stress* oxidativo, tabagismo, alterações das trocas gasosas, alterações nutricionais, redução dos níveis de hormonas anabolizantes, ao envelhecimento e ao uso de corticosteróides [23, 86].
- **Limitação cardiovascular** – habitualmente por sobrecarga do ventrículo direito decorrente da hipoxemia e da hipertensão arterial pulmonar. O ventrículo esquerdo também pode ser afetado quando existe desvio do septo decorrente da dilatação do ventrículo direito. As disritmias e a elevação da pressão na aurícula direita devida ao *air-trapping* também podem limitar a capacidade para o exercício [23, 82].

Os **benefícios fisiológicos do treino** ao nível do **sistema respiratório** podem ser avaliados com uma prova de *endurance* de carga constante, em que, na prova realizada após o treino, se verifica melhoria da cinética da captação do oxigénio, da depuração de dióxido de carbono e uma redução da ventilação minuto para a mesma carga [87]. O padrão ventilatório é otimizado, com aumento do volume corrente e redução da frequência respiratória, o que reduz a ventilação de espaço morto e se associa a melhor tolerância ao exercício [87].

Com o treino aeróbio, o maior retorno venoso conduz, pela lei de Frank-Starling, a uma dilatação ou hipertrofia excêntrica dos ventrículos e a consequente aumento do volume sistólico e do débito cardíaco. Estas **adaptações cardiocirculatórias** ao treino aeróbio levam à redução da frequência cardíaca em repouso e no exercício de intensidade ligeira a moderada [88].

As **adaptações musculares** ao treino de exercício incluem a hipertrofia muscular, com aumento das fibras musculares glicolíticas de tipo 2b, no caso do treino de força e aumento das fibras lentas oxidativas (de tipo 1 e 2a), com maior riqueza em mitocôndrias e na proporção de capilares em cada fibra muscular, no treino de *endurance* [89, 90].

Princípios do treino de exercício

Para otimizar os efeitos do treino de exercício, é necessário respeitar os seus princípios fisiológicos [88]:

Princípio da sobrecarga: a aplicação de uma sobrecarga num exercício específico, melhora a função e a resposta ao treino.

Princípio da especificidade: as adaptações metabólicas e fisiológicas do treino dependem do tipo e modalidade de sobrecarga imposta. Por exemplo, o treino de força muscular induz aumento da força e o treino de *endurance* muscular resulta em melhoria predominante da *endurance*. Para respeitar o princípio da especificidade, a avaliação dos efeitos do treino realizado num determinado ergómetro (exemplo, tapete rolante, bicicleta ou remo) deve preferencialmente ser feita com o mesmo equipamento.

Princípio das diferenças individuais: um determinado estímulo de treino induz diferentes respostas em indivíduos diferentes. Os fatores genéticos, a aptidão prévia e as necessidades e capacidades individuais são variáveis que determinam as diferentes respostas ao treino e devem ser respeitadas na programação dos mesmos.

Princípio da reversibilidade: quando se deixa de treinar, verifica-se uma perda das adaptações fisiológicas e do desempenho obtidos com o treino. Este efeito pode observar-se, por exemplo, a partir das três semanas após a suspensão de um treino de *endurance*.

Modalidades do treino de exercício:

De acordo com os princípios do treino acima enunciados, as modalidades do treino devem ser programadas para que o volume de treino (frequência, duração, intensidade) se adeque a cada indivíduo, excedendo as cargas habituais da sua rotina diária (progressão do treino) e, dessa forma, melhorar a capacidade aeróbica e a força muscular [23].

Treino de *endurance*, contínuo ou intervalado – tem por objetivo aumentar a capacidade de *endurance* (resistir à fadiga) em exercícios que envolvem as grandes massas musculares (exercícios de caraterísticas gerais, como a dança, caminhada, bicicleta, corrida - Figura 1) ou por grupos musculares (exercícios de caraterísticas locais, como o treino de endurance muscular dos membros superiores ou dos membros inferiores).

Figura 1: Treino aeróbico em tapete rolante e em bicicleta

Em doentes com patologia respiratória crónica são habitualmente recomendados treinos de *endurance* de elevada intensidade (60-80% da potência aeróbica máxima), em regime contínuo durante 20 a 60 minutos por sessão, 3 a 5 vezes por semana [84, 91]. Em doentes com dificuldade em tolerar o treino contínuo, por intensa dispneia, hiperinsuflação pulmonar dinâmica ou fadiga [92], pode optar-se por um treino intervalado, em que períodos de 1 a 2 minutos de duração, de exercícios a elevada intensidade (80 a 120% da capacidade máxima) alternam com períodos similares de exercício de baixa intensidade ou de repouso [93].

O atraso da ocorrência da acidose láctica, observada com o treino de *endurance*, contínuo ou intervalado, permite a redução do comando ventilatório, reduzindo assim a dispneia e a fadiga muscular periférica [94, 95].

Treino de força – Com o recurso a aparelhos de musculação, pesos, elásticos de diferentes resistências ou ao peso do próprio corpo, o treino de força tem como resultado o aumento da massa e da força musculares, permitindo aos doentes respiratórios melhorar a capacidade de exercício para as atividades diárias que requerem o uso da força, diminuir o recurso aos cuidados de saúde e melhorar a qualidade de vida e a esperança de vida [96, 97] (Figura 2). Na RR, os exercícios podem ser realizados em aparelhos com cargas elevadas, equivalentes a 70 a 85% de uma repetição máxima, realizando exercícios com 8 a 10 repetições, duas a três sessões por semana, ao longo de 8 a 12 semanas [84].

Figura 2: Treino de força – extensão dos membros inferiores

O **treino combinado** (aeróbico e de força) associa os benefícios de ambas as modalidades, sendo recomendado para doentes com patologia respiratória [98, 99].

Algumas **estratégias e modalidades** adotadas com o objetivo de **otimizar os efeitos do treino** são, entre outros, a oxigenoterapia em situações de dessaturação significativa com o exercício; a ventilação não invasiva em doentes com limitação ventilatória grave; o treino em circuito envolvendo alternadamente os diferentes grupos musculares e o treino dos músculos inspiratórios em doentes com importante fraqueza destes músculos [74]. Este pode ser realizado em sessões de 15 minutos, duas vezes por dia, a uma intensidade de pelo menos 30% da pressão inspiratória máxima [84].

Fazem igualmente parte dos programas de RR, o treino de atividades da vida diária [23], as técnicas de conservação de energia [100], e o treino de equilíbrio e de flexibilidade [91, 101, 102].

Em doentes com elevada incapacidade, acamados, após internamentos prolongados ou em cuidados intensivos, a estimulação elétrica neuromuscular tem o potencial de contrariar a perda da massa muscular e da força associadas à inatividade [59, 103, 104].

Benefícios e resultados dos programas

Os programas de RR conduzem a benefícios com comprovada evidência científica. Esta pode ser classificada de acordo com a qualidade dos resultados dos estudos, em evidência A (estudos controlados e aleatorizados com elevado número de doentes), evidência B (estudos controlados e aleatorizados com menor número de doentes), evidência C (estudos não aleatorizados e estudos observacionais) e evidência D (estudos de opinião de painel de peritos) [71].

Os benefícios da RR em doentes com DPOC com evidência A são: a melhoria da capacidade de exercício, melhoria da dispneia, melhoria da qualidade de vida relacionada com a saúde (ou estado de saúde), redução da ansiedade e depressão relacionadas com a DPOC e redução de hospitalizações e sua duração [71]. São evidências B, a melhoria da função muscular dos membros superiores após treino de força e de *endurance*, o prolongamento dos benefícios após o período imediatamente a seguir ao

treino, a melhoria da esperança de vida, a recuperação mais rápida após exacerbações graves, e a potenciação do efeito dos broncodilatadores de ação prolongada [71].

A duração mínima dos programas para obtenção de benefícios é de 6 a 8 semanas [23]. Contudo, os programas mais longos têm maiores benefícios. Por exemplo, a melhoria da capacidade para o exercício funcional verifica-se habitualmente após 3 meses de reabilitação, enquanto o aumento dos níveis de atividade física se observa após 6 meses [105].

Tendo em conta os objetivos definidos pela iniciativa GOLD para o tratamento da DPOC [71], verifica-se que os resultados obtidos com os programas de RR cumprem a maior parte daqueles objetivos:

- Alívio sintomático, em particular, a dispneia associada ao exercício [106] e a dispneia associada às atividades da vida diária [107, 108].
- Melhoria da capacidade de exercício, incluindo a capacidade para o exercício máximo, o consumo de oxigénio de pico, a capacidade de *endurance* em testes submáximos, a capacidade funcional na marcha e a força dos músculos periféricos e dos músculos respiratórios [38].
- Melhoria do estado de saúde, avaliada por questionários gerais [109] e por questionários específicos de doença [110, 111], excedendo habitualmente os valores limite considerados clinicamente importantes nos questionários específicos de doença. São exemplo as melhorias nos domínios sintomas, atividade e impacto no questionário de doenças respiratórias de St. George ou nos domínios dispneia, fadiga, função emocional e controlo no questionário de doenças respiratórias crónicas.
- Prevenção de complicações e exacerbações [36], resultando em diminuição da utilização dos recursos de saúde [112] e dos custos [113], podendo considerar-se uma intervenção custo-efetiva [21].
- Redução da mortalidade em programas de RR realizados após exacerbações recentes [36, 113].
- Redução da progressão da doença. Sendo mais difícil de aferir diretamente este resultado, ele pode contudo decorrer dos outros resultados: na melhoria dos sintomas, capacidade de exercício, estado de saúde e na menor utilização dos recursos de saúde.

Limitações

São conhecidos alguns fatores que condicionam a realização dos programas de RR, nomeadamente a não adesão dos doentes e a falta de acessibilidade. O isolamento social, a depressão e a fraqueza muscular do quadricípite associam-se à não adesão [57]. Um estudo retrospetivo mostrou que tinham maior probabilidade de não completar o programa, os doentes com DPOC que ainda mantinham hábitos tabágicos, os que estavam integrados em programas de RR de longa duração, os que tiveram exacerbações frequentes no ano anterior, os que residiam a grande distância do centro de reabilitação e os que tinham maior grau de dispneia [114]. Por estes motivos, a taxa de abandonos dos programas situa-se habitualmente entre 20 a 30%. Apesar de elevada, esta taxa de abandonos não atinge a que habitualmente é atribuída à população saudável. Cerca de 50% das pessoas que iniciam um programa de exercício irão abandonar esse programa nos primeiros 6 meses [115].

A baixa taxa de referenciação para RR, o número elevado de doentes em lista de espera, a reduzida oferta de unidades de RR ou a sua capacidade, o défice económico e a distância da residência dos doentes aos locais de tratamento, podem contribuir para dificultar a acessibilidade aos programas de RR.

A doença pulmonar obstrutiva crónica

O facto de a DPOC ser uma doença frequente e com elevado impacto clínico, social e económico, justifica que seja esta a doença em que mais estudos científicos se desenvolveram sobre o papel da reabilitação respiratória.

A DPOC é uma doença comum, que se pode prevenir e tratar. A sua componente pulmonar consiste numa limitação persistente e habitualmente progressiva do débito aéreo, associada a uma resposta inflamatória anómala das vias aéreas inferiores e do parênquima pulmonar por exposição a gases ou partículas nocivas [116]. A doença tem igualmente uma componente multissistémica, podendo envolver, entre outros, o sistema musculo-esquelético, alterações nutricionais e metabólicas, cardiovasculares, ou psicológicas, como a depressão e a ansiedade [117, 118]. As exacerbações e as comorbilidades contribuem para a gravidade global em cada doente [116].

A DPOC constitui atualmente um importante problema de saúde pública, já que afeta cerca de 210 milhões de pessoas em todo o mundo, estimando-se uma mortalidade anual de 300 mil doentes na Europa [61] e com custos económicos significativos decorrentes do agravamento progressivo da doença, com hospitalizações e readmissões hospitalares frequentes [116, 119].

A prevalência da DPOC varia nas diferentes regiões do mundo, entre 3,6% em Barranquilla, na Colômbia e 19% em Cape Town, na África do Sul [120]. O valor mais elevado da prevalência, 23%, encontra-se nos homens com 40 ou mais anos em Cape Town, África do Sul [121].

Os dados disponíveis evidenciam que a variabilidade encontrada na prevalência da DPOC nos vários países pode ser atribuída às diferentes metodologias utilizadas, nomeadamente nos critérios diagnósticos [122].

O elevado subdiagnóstico da DPOC é evidente quando baseado no conhecimento do doente – só cerca de 6% dos doentes referem ter um diagnóstico médico de DPOC [122]. Os fatores que se associam ao subdiagnóstico da DPOC são a idade mais jovem, ser do género masculino, não fumador ou fumador ativo, ter baixa literacia, ausência de espirometria prévia e uma menor gravidade na obstrução das vias aéreas [120].

A DPOC apresenta uma prevalência mais elevada com a idade, em particular a partir dos 40 anos, sendo mais frequente em fumadores e ex-fumadores [122, 123]. Contudo, em não fumadores, está documentada uma prevalência entre 3 e 11% [124].

Na maior parte dos estudos, a prevalência é maior em homens [122, 123, 125]. São exceção os estudos BOLD realizados em Salzburg [126], em que a prevalência é igual em ambos os sexos, e nos EUA [127], em que as mulheres reportam ter DPOC em maior número que os homens.

Prevalência da DPOC em Portugal

À semelhança do que acontece em outros países [128, 129], existe ainda em Portugal um elevado défice de conhecimento relativo à DPOC [130] o que tem como consequência o subdiagnóstico da doença.

Com o objetivo de sensibilizar para o diagnóstico da DPOC e para o papel da espirometria no diagnóstico precoce, foi realizado entre maio de 2007 e maio de 2008, o estudo Pneumobil-2, dirigido a 5324 indivíduos fumadores e ex-fumadores com 40 ou mais anos [130]. Verificou-se uma prevalência de obstrução brônquica de 25% nesta população considerada de elevado risco, dos quais, apenas 5% tinham conhecimento da doença [130].

Desde 1995 têm sido realizados em Portugal vários estudos para estimar a prevalência da DPOC. O estudo Pneumobil-1 decorreu entre 1995 e 1997 em 17 distritos de Portugal continental, aplicando um questionário adaptado do Questionário de doenças respiratórias da *American Thoracic Society* [131] e realizando espirometria antes e após a administração de broncodilatador inalado. Os participantes dirigiram-se voluntariamente aos locais públicos onde se realizou a colheita dos dados. Foram considerados elegíveis 9061 indivíduos com 40 ou mais anos, dos quais 8,96% apresentava obstrução brônquica não reversível (11,9% no sexo masculino e 5,9% no sexo feminino) [132]. Uma limitação patente neste estudo residia no facto de existir enviesamento na amostra de indivíduos. Pelo facto de se tratar de voluntários, o estudo não teve o desejável carácter aleatório [132].

Entre outubro de 2001 e março de 2002 foi realizado um novo estudo para estimar a prevalência da DPOC, desta vez, em todos os distritos de Portugal continental. A amostra foi selecionada aleatoriamente a partir dos contactos das listas telefónicas, em indivíduos entre os 35 e os 69 anos. Ao aceitarem participar, era agendada a data e hora para a colheita de dados (questionário e espirometria). A Comissão de Ética do estudo não permitiu a administração de fármacos, pelo que se realizou apenas o estudo espirométrico basal. A exclusão de doentes com asma foi realizada mediante as respostas dadas no questionário. Dos 1384 indivíduos elegíveis, 5,34% apresentavam obstrução brônquica (6,3% no género masculino e 4,5% no género feminino) [132].

Apesar de neste estudo, a amostra ter sido considerada representativa da população portuguesa, o facto de não ter sido avaliada a espirometria após a administração de broncodilatador, dificultou o rigor no diagnóstico da DPOC, à luz dos conhecimentos atuais [116]. Além disso, a exclusão de indivíduos com 70 ou mais anos, contribuiu seguramente para subestimar o valor da prevalência da DPOC, já que esta aumenta com a idade e o conhecido envelhecimento da população prevê que muitos doentes com DPOC possam ter sido excluídos do estudo.

A importância do conhecimento rigoroso do valor da prevalência da DPOC em Portugal impõe-se pelas recomendações da iniciativa GOLD [116] que salientam a necessidade de conhecer a dimensão do problema em cada região, para assim sensibilizar a população, os profissionais de saúde, as autoridades de saúde e os governos e alocar os meios para a sua correção.

Atendendo às limitações apontadas aos estudos anteriores, impôs-se a realização de um novo estudo, seguindo desta vez o protocolo cumprido pelo BOLD (*Burden of Obstructive Lung Disease*) a nível internacional [133]. Este constituiu o **Estudo 1** desta tese (Capítulo 4).

Mortalidade

O estudo do impacto global das doenças publicado por Murray em 1997 indicava a DPOC como a 6ª principal causa de morte mundial em 1990, projetando elevar-se para

3ª em 2020 [134]. Em 2006, Mathers e Loncar alteram esta projeção para 4ª causa em 2030 [135]. A Organização Mundial de Saúde em 2008, projeta a DPOC como 3ª principal causa de morte mundial em 2030 [136].

Na realidade, desde 2011 que a DPOC constitui já a 3ª principal causa de morte em países desenvolvidos, por exemplo, nos Estados Unidos da América [137]. Na Europa, 18 por 100 mil habitantes morrem por ano devido à DPOC [138]. Em Portugal, a mortalidade devida à DPOC era, em 2013, de 14 por 100 mil habitantes por ano [138].

Existem diferenças, entre ambos os sexos, na taxa de mortalidade. Nos Estados Unidos da América, embora ainda seja superior nos homens, a diferença na taxa de mortalidade entre os sexos, tem vindo a reduzir-se nos últimos anos, de 54,4 por 100000 habitantes em 1976 para 16,2 por 100000 habitantes em 2011, refletindo um declínio nos homens, desde 1999 e uma subida mantida nas mulheres [139].

A elevada mortalidade é atribuída à epidemia do tabaco, ao envelhecimento da população mundial e, em termos relativos, à redução da mortalidade por outras causas comuns de morte, como por exemplo, as doenças cardiovasculares e as doenças infeciosas [116]. O défice económico associa-se igualmente a elevada mortalidade por DPOC, bem como a um padrão espirométrico de restrição [121]. Em países subdesenvolvidos, esta associação poderá ser explicada por vários fatores, como o baixo peso à nascença, a dieta pobre, as infeções respiratórias na infância, a exposição precoce a poluição dentro de casa por combustão de biomassa ou a presença de comorbilidades [121].

É igualmente conhecido o impacto das exacerbações sobre a mortalidade [140], em particular, o mau prognóstico a longo prazo associado às exacerbações graves: 5 anos após uma hospitalização por exacerbação de DPOC, a taxa de mortalidade chega a ser de 50% [141].

Os doentes com DPOC em fase avançada que são referenciados para reabilitação respiratória, referem habitualmente sintomas incapacitantes como a dispneia para pequenos esforços, a intolerância para as atividades físicas diárias, a tosse ineficaz e apresentam frequentemente défice muscular (atrofia e fraqueza musculares), desnutrição, e outras comorbilidades significativas [90, 142]. A evolução para insuficiência respiratória crónica e respetivo tratamento (oxigenoterapia e ventiloterapia) acrescentam um impacto negativo para o dia-a-dia destes doentes.

Nesta fase avançada da doença, a esperança de vida dos doentes é geralmente reduzida, devido não apenas à gravidade da doença e ao impacto das exacerbações, como também às comorbilidades frequentes [18, 143].

Importa conhecer quais os fatores associados ao doente – aspetos clínicos e funcionais – que possam prever a mortalidade. Em particular, o conhecimento de fatores potencialmente modificáveis, poderá ser um contributo para, após a sua correção, modificar a evolução negativa da doença. Este constituiu o **Estudo 2** desta tese (Capítulo 4).

Morbilidade e impacto na capacidade funcional

Os fatores que se associam de forma independente a um pior prognóstico incluem a idade avançada, um menor índice de massa corporal, as comorbilidades como a doença cardiovascular ou o cancro do pulmão, internamentos prévios por exacerbação da DPOC, gravidade da exacerbação e necessidade de oxigenoterapia de longa duração no momento da alta [144, 145]. Após uma exacerbação aguda de DPOC, os doentes com maior risco de mortalidade são os que apresentam prevalência mais elevada e maior gravidade de sintomas respiratórios, pior qualidade de vida, pior função respiratória, menor capacidade funcional, menor densidade pulmonar e paredes brônquicas espessadas na tomografia computorizada [146].

Prevê-se que nas próximas décadas o impacto negativo da DPOC seja agravado devido ao envelhecimento das populações e à exposição mantida aos fatores de risco [135, 147]. Segundo as projeções baseadas nos DALYs [116] (*Disability-Adjusted Life Years* ou a perda de anos de vida por mortalidade prematura associada à DPOC e o número de anos de vida com incapacidade), a DPOC passará de 12ª doença com maior incapacidade a nível mundial em 1990 para 7ª em 2030 [135].

A perda progressiva da capacidade que os doentes com DPOC têm para a realização das atividades físicas da vida diária, sublinha a necessidade de identificar precocemente o risco destes doentes se tornarem dependentes, para que se possam desenvolver estratégias de prevenção e tratamento adequados. Este constituiu o **Estudo 3** desta tese (Capítulo 4).

A inflamação sistémica e a DPOC

A doença pulmonar obstrutiva crónica caracteriza-se pela presença de uma limitação do débito, resultante da inflamação e remodelação das vias aéreas frequentemente associadas à destruição parenquimatosa e ao desenvolvimento de enfisema [148].

Associa-se a importantes manifestações extrapulmonares, incluindo perda de peso, disfunção do músculo esquelético, doença cardiovascular, síndrome depressiva, osteoporose, redução da tolerância ao exercício e perda de qualidade de vida [149, 150].

Embora o conhecimento dos mecanismos patogénicos da DPOC não seja completo, a inflamação sistémica tem sido implicada na patogénese da maioria dos efeitos sistémicos [150], o que levou alguns autores a sugerir que a DPOC faz parte da síndrome da inflamação sistémica crónica [149]. A inflamação sistémica persistente de baixo grau parece ter um papel importante na patogénese da DPOC e associa-se a uma redução da função respiratória [151].

Têm sido reportados em doentes com DPOC níveis elevados de leucócitos circulantes, de proteína C reativa, de interleucinas 6 (IL-6) e 8 (IL-8), de fibrinogénio e de fator de necrose tumoral alfa (TNFα) [152].

Contudo, tal como evidenciaram vários estudos, a inflamação sistémica não está presente num grande número de doentes com DPOC [153, 154].

O papel do exercício no processo inflamatório da doença também tem sido discutido. Os doentes com DPOC estão expostos a inflamação sistémica que é ampliada pelo exercício intenso. A resposta inflamatória ao exercício é mais pronunciada em doentes com DPOC quando comparados com controlos saudáveis, mesmo para exercícios de baixa intensidade [155, 156]. Contudo, também aqui a literatura científica não tem sido consensual, já que vários estudos evidenciaram uma redução da expressão da proteína TNFα em doentes com DPOC [157-159].

Tal como sugeriram Canavan e colaboradores, alguma da heterogeneidade presente nestes resultados pode advir do fato de se utilizarem diferentes metodologias nos vários estudos realizados (ex. na caracterização dos doentes, nos protocolos do exercício e nas técnicas laboratoriais) [160].

Crul e colaboradores não encontraram evidência de inflamação muscular em doentes com DPOC, independentemente de se encontrarem em fase estável ou em fase de exacerbação da doença [161]. No outro extremo, alguns autores sugerem um efeito anti-inflamatório do exercício físico regular em algumas doenças crónicas com inflamação de baixo grau, o que poderá levar a resultados benéficos na prevenção da doença e na melhoria sintomática [162, 163].

É importante esclarecer em doentes com DPOC, qual a expressão da inflamação avaliada em repouso e a sua eventual modificação após o exercício físico, bem como pesquisar características dos doentes que se associem a essa expressão inflamatória. Este constituiu o **Estudo 4** desta tese (Capítulo 4).

Programas de reabilitação respiratória

Em doentes com DPOC, de acordo com a classificação A, B, C e D

Os programas de RR são dirigidos aos doentes respiratórios crónicos sintomáticos, que apresentam limitação da função respiratória ou intolerância ao esforço, apesar da otimização da terapêutica farmacológica [24, 72, 164]. Estas indicações abrangem, potencialmente, todos os doentes com DPOC, já que as suas limitações mais frequentes são a limitação ventilatória, pela dispneia e/ou a hiperinsuflação pulmonar e a disfunção muscular dos músculos da deambulação [82].

A maior parte dos doentes com DPOC referenciados para RR apresentam obstrução brônquica grave e muito grave, ou uma limitação importante na capacidade de exercício para as atividades da vida diária. Evidências recentes têm vindo a demonstrar que mesmo em doentes com obstrução moderada, os benefícios são igualmente significativos e podem verificar-se, independentemente do grau de gravidade da obstrução das vias aéreas [89, 165]. Mas a DPOC, sendo uma doença que afeta primariamente o aparelho respiratório, tem igualmente efeitos sistémicos e a caraterização do seu grau de gravidade fica limitada, quando somente a função respiratória é incluída nesta equação.

Desde 2011 que o projeto mundial GOLD (*Global Initiative for Obstructive Lung* Diseases) introduziu uma nova classificação da gravidade da DPOC, atribuindo 4 graus de gravidade, de A a D (Figura 3) [71].

Apesar de não incluir alguns aspetos importantes da doença, nomeadamente a presença de comorbilidades e a limitação da tolerância ao esforço, a nova classificação da DPOC avalia o risco de mortalidade pela gravidade da obstrução das vias aéreas e pela ocorrência de exacerbações, e avalia os sintomas pelo grau de dispneia e o impacto da doença no estado geral de saúde pelo questionário CAT ou *COPD Assessment Test*, daqui resultando uma maior complexidade e heterogeneidade de diferentes subgrupos de caraterísticas [166].

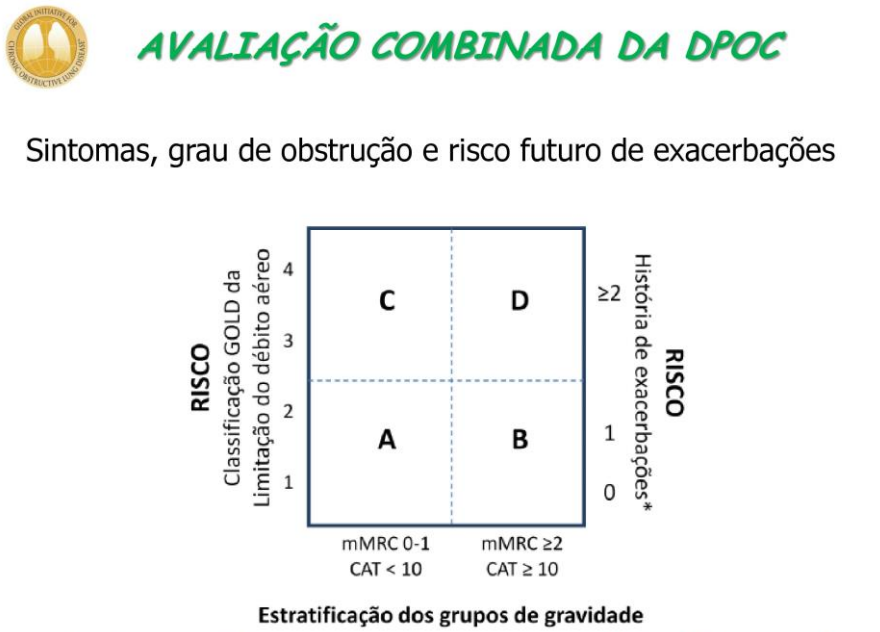

Figura 3: Classificação da DPOC associando os sintomas, o grau de obstrução brônquica e o risco futuro de exacerbações (*GOLD updated 2011)*

Esta classificação é mais abrangente do que a anterior e os componentes que foram adicionados, nomeadamente os sintomas, o estado geral de saúde e a ocorrência das exacerbações, são potencialmente modificáveis com os programas de reabilitação [38].

Apesar dos programas de RR serem considerados intervenções com uma boa relação custo-eficácia [21], eles não estão ainda suficientemente disseminados e acessíveis a todos os doentes que dele necessitam. Importa assim caraterizar quais os doentes que melhor beneficiam dos programas de RR.

Com este objetivo, procedemos a um estudo de avaliação dos efeitos da RR em cada subgrupo de doentes dos graus GOLD A, B, C e D. Este constituiu o **Estudo 5** desta tese (Capítulo 4).

Impacto das comorbilidades da DPOC nos resultados da reabilitação respiratória

A DPOC é uma doença complexa, heterogénea e multicomponente [166], afetando não apenas o sistema respiratório, mas apresentando efeitos extrapulmonares significativos que contribuem para a sua gravidade [167, 168]. A presença de comorbilidades é hoje reconhecida como causa de agravamento dos sintomas, da qualidade de vida e da capacidade funcional em doentes com DPOC, aumentando o risco de hospitalizações e de mortalidade [168]. As comorbilidades mais frequentemente associadas à DPOC são as doenças cardiovasculares, como a hipertensão arterial, a insuficiência cardíaca, a doença coronária, as arritmias, a doença cerebrovascular e a doença vascular periférica; as doenças metabólicas como a diabetes mellitus, a dislipidemia, o excesso de peso ou obesidade; as doenças respiratórias, como as sequelas pleuropulmonares de tuberculose pulmonar, as bronquiectasias, a síndrome de apneia obstrutiva do sono, as doenças do interstício pulmonar e o cancro do pulmão [169]; a osteoporose e a patologia osteoarticular; a síndrome ansiosa/depressiva, entre outras [170]. Tendo em conta o impacto negativo das comorbilidades na gravidade e no prognóstico da DPOC, importa saber reconhecê-las e tratá-las. Assim, o tratamento da DPOC não deve limitar-se à prescrição de broncodilatadores e à prevenção de exacerbações, devendo ser mais abrangente e holístico, incluindo o diagnóstico e tratamento das manifestações sistémicas e das comorbilidades associadas à DPOC [171].

A RR tem como objetivo melhorar os sintomas, a qualidade de vida, a tolerância ao exercício, aumentar a participação dos doentes nas atividades diárias e diminuir a utilização dos recursos de saúde (consultas não programadas, idas às urgências, hospitalizações, etc.) dos doentes com patologia respiratória crónica [23]. Importa conhecer a prevalência das comorbilidades na população de doentes que são referenciados para reabilitação respiratória e avaliar a influência das comorbilidades nos resultados dos programas de RR. Este constituiu o **Estudo 6** desta tese (Capítulo 4)..

Efeitos de duas intensidades de treino aeróbio nos resultados centrados no doente – estudo controlado e aleatorizado

Os efeitos fisiológicos do treino de exercício são dose-dependentes [172]. Esta afirmação, aplicada aos programas de reabilitação com treino de exercício em doentes com DPOC, surgiu desde os trabalhos de Casaburi em 1991, com a evidência de maiores benefícios fisiológicos após o treino aeróbio de intensidade mais elevada, realizado a 80% da potência aeróbica máxima (Wmax), comparado com o treino com intensidade moderada, a 50% da Wmax [14, 87]. No primeiro caso, verificou-se maior redução do lactato arterial, da ventilação minuto, do consumo de oxigénio, da produção de dióxido de carbono, do equivalente metabólico de oxigénio e da frequência cardíaca.

Apesar da intensidade ótima de treino ainda não estar definitivamente estabelecida, têm sido atribuídos benefícios fisiológicos mais significativos, quanto maior a intensidade dos treinos, a partir de 60% da potência aeróbica máxima (Wmax) [173, 174].

Contudo, ainda não foi provado de forma conclusiva que os benefícios fisiológicos do treino aeróbio, como o atraso da ocorrência do limiar anaeróbico, a redução da ventilação ou a redução da frequência cardíaca se associem a melhoria significativa dos resultados centrados no doente, como por exemplo, a qualidade de vida, ou a dispneia [24]. Além disso, alguns doentes não toleram o treino a elevadas intensidades e a adesão a longo prazo pode ser maior se o treino for realizado a intensidades mais baixas [24].

Dos benefícios obtidos com os programas de RR, os que têm um impacto positivo mais significativo para os doentes, são a melhoria nos sintomas, na capacidade para o exercício e na qualidade de vida [23].

Tendo em conta as intensidades de treino atualmente recomendadas a partir de 60% da potência aeróbica máxima [23], levanta-se a questão se a uma maior intensidade de treino aeróbio (80% Wmax *versus* 60% Wmax) correspondem melhores resultados centrados no doente. Esta foi a questão investigada no **Estudo 7** desta tese (Capítulo 4) e constituiu o tema da Tese de Mestrado da licenciada Catarina Santos, da qual fui coorientadora.

Importância da atividade física na DPOC

Fatores que influenciam a atividade física diária

"A falta de atividade destrói a boa condição de qualquer ser humano, enquanto que o movimento e o exercício físico metódico, salva-a e preserva-a". Platão (427-347 a.C.) [79]

A sociedade contemporânea convida ao sedentarismo, já que a maior parte das profissões atuais obrigam a estar sentado num elevado número de horas, por exemplo, em frente a um computador e o desenvolvimento tecnológico com a utilização de dispositivos de controlo remoto permite, entre outros "benefícios", "viajar" sem sair do sofá. Esta tendência global para o sedentarismo, hoje apelidada de "nova epidemia tabágica", tem sido responsável por um conjunto de doenças ditas "da civilização" tais como a obesidade, a hipertensão arterial ou o cancro e contribui para cerca de 9% da mortalidade prematura [175, 176].

Pode definir-se o sedentarismo como qualquer comportamento que ocorre durante as horas de vigília, em que o dispêndio energético é inferior a 1,5 METs (equivalentes metabólicos das tarefas), em posição de sentado ou deitado [177]. Inclui-se neste conceito, as horas passadas a trabalhar sentado ou a ver televisão. Um indivíduo é considerado inativo quando não cumpre as recomendações mínimas da atividade física por exemplo, caminhar 30 minutos por dia, três vezes por semana [177]. Pode ser-se sedentário várias horas ao longo do dia e contudo cumprir os critérios de atividade física em outros momentos do dia. Ambos os comportamentos, sedentarismo e inatividade, acarretam riscos para a saúde [178]. As recomendações atuais vão no sentido de aumentar a atividade física e de reduzir os comportamentos sedentários [179].

Nos doentes com patologia respiratória crónica é ainda mais fácil admitir que sintomas como a dispneia, conduzam inevitavelmente a uma perda da capacidade para realizar exercício físico.

A DPOC é uma condição com efeitos que vão para além do sistema respiratório, afetando nomeadamente a função e a estrutura dos músculos esqueléticos e somando ao fator dispneia, o descondicionamento muscular e o sedentarismo [84]. Hoje é reconhecida a redução significativa da atividade física regular em doentes com DPOC, mesmo em fases precoces da doença [180, 181]. A proporção de hábitos sedentários é significativamente

superior nos doentes no estádio GOLD 1 comparando com doentes com bronquite crónica simples e a proporção de doentes muito inativos aumenta consideravelmente nos estádios GOLD 3 e 4 [180]. Quando se comparam com controlos saudáveis, os doentes com DPOC passam muito mais tempo sentados e deitados e caminham menos e mais lentamente [181].

Um dos fatores que tem um impacto significativo na atividade física são as exacerbações da DPOC. Após as exacerbações, os doentes apresentam fraqueza muscular, ficam inativos, perdem *status* funcional, o que os torna mais vulneráveis a reinternamentos [182].

Em doentes com DPOC, os estudos indicam o sedentarismo como um fator prognóstico significativo, apresentando um risco de mortalidade aos 4 anos de 31% [183]. Estes aspetos sublinham a necessidade de conhecer os fatores que se associam à menor atividade física, procurando nomeadamente, aqueles que são potencialmente modificáveis, para que sejam implementadas estratégias terapêuticas adequadas à sua correção. Este foi o objetivo do **Estudo 8** desta tese (Capítulo 4) e constituiu o tema da Tese de Mestrado da licenciada Susana Barriga, da qual fui coorientadora.

Evolução da capacidade funcional e estado de saúde dois anos após um programa de reabilitação respiratória

Os programas de reabilitação respiratória com treino de exercício têm demonstrado vários benefícios para o doente com DPOC, sendo um dos mais significativos, a melhoria da tolerância ao esforço, o que se reflete na maior capacidade para a realização das atividades físicas da vida diária, quer em termos da força, quer da capacidade para resistir à fadiga, com melhoria da qualidade de vida relacionada com a saúde [23, 38].

Os benefícios obtidos com os programas de treino de exercício, na melhoria da condição física têm uma duração variável, podendo estes efeitos prolongar-se mais, quando os programas são mais longos [108, 184].

Contudo, após terminar o programa de treino, uma parte dos doentes reduz substancialmente os níveis de atividade física e, em alguns casos, regressa até aos

hábitos anteriores de sedentarismo e inatividade, perdendo progressivamente os benefícios obtidos com o treino [185]. Este fenómeno é explicado por um dos princípios gerais da metodologia do treino: o princípio da reversibilidade, segundo o qual, quando se deixa de treinar, se verifica uma perda das adaptações fisiológicas e do desempenho obtidos com o treino [88].

Ao longo dos programas de RR, os doentes são incentivados a adotar estratégias de aumento geral da atividade física regular, por forma a manterem-se ativos quando os programas supervisionados pelos técnicos terminam (Figura 4).

Figura 4: Caminhada com oxigénio de deambulação

Contudo, existem barreiras de vários tipos que impedem os doentes de adotar esses hábitos. Alguns fatores, como a hiperinsuflação pulmonar, a dispneia, a alteração das trocas gasosas, as exacerbações prévias, a inflamação sistémica, a qualidade de vida e a autoeficácia apresentam associação consistente com a atividade física [79, 186]. Outros fatores como a falta de tempo, de autoconfiança, de segurança, de suporte familiar ou comunitário, o clima agreste, as barreiras físicas, como os pavimentos irregulares ou ruas inclinadas, têm sido apontados como barreiras à atividade física regular [187].

Importa esclarecer qual o impacto da manutenção da atividade física regular ou a ausência dela, após terminar um programa de RR, nos benefícios para a saúde. São avaliados: a capacidade de exercício funcional pela distância na prova de marcha de 6 minutos e a qualidade de vida relacionada com a saúde pelo questionário de doenças respiratórias de St. George. Esta questão deu origem ao **Estudo 9** desta tese (Capítulo 4).

O projeto TelemOLD: sistema de telemonitorização que combina a oximetria e a quantificação da atividade física para uma melhor adequação da oxigenoterapia de longa duração

A perda progressiva da capacidade para o exercício, verificada após a fase intensiva dos programas de treino, pode ser atenuada, se os doentes mantiverem algum grau de atividade física regular. Contudo, em doentes com DPOC em fase avançada da doença, a evolução para insuficiência respiratória crónica contribui significativamente para a tendência ao sedentarismo. Este resulta da maior limitação respiratória, pela gravidade das alterações funcionais e estruturais pulmonares, pelas comorbilidades tão frequentemente associadas, como as alterações nutricionais (ex. caquexia, atrofia muscular) e as comorbilidades cardiovasculares (ex. *cor pulmonale* crónico ou a insuficiência cardíaca congestiva). Pode resultar ainda do efeito nocivo da hipoxia crónica sobre os órgãos e sistemas (incluindo o muscular esquelético), e ainda, pelo impacto da terapêutica, pela complexidade dos dispositivos de oxigenoterapia e/ou ventiloterapia domiciliários, constituindo para alguns doentes, mais um fator que dificulta a adoção de hábitos de exercício regular.

Se por um lado, a atividade física regular é hoje reconhecida como um dos hábitos de vida saudáveis com melhor impacto prognóstico [183, 186], a oxigenoterapia de longa duração em doentes com insuficiência respiratória crónica e hipoxemia grave provou desde os anos 80, ser uma terapêutica com benefícios, não só na melhoria da tolerância ao exercício, mas também na redução do número de hospitalizações e no aumento da esperança de vida [188].

É contudo importante salientar que os benefícios atribuídos à oxigenoterapia nestes doentes só se verificam se esta terapêutica for cumprida durante pelo menos 15 horas por dia [189], sendo os benefícios superiores se for administrada continuamente [190]. A aferição dos débitos de oxigénio para as diferentes situações ao longo do dia, em repouso, no esforço e durante o sono, é habitualmente realizada em meio hospitalar, com o recurso a gasometrias arteriais seriadas, a provas de marcha de 6 minutos e, durante o sono, através de oximetrias noturnas no doente eletivamente internado.

Quando realizadas no domicílio dos doentes, as aferições do débito de oxigénio requerem habitualmente 2 ou 3 noites de registo.

Uma correta aferição das necessidades reais em oxigénio permitirá ajustar a terapêutica às diferentes exigências físicas e/ou ventilatórias das atividades da vida diária. A monitorização dos valores de oximetria em tempo real avaliada nos doentes no seu meio domiciliar ou profissional constituirá uma vantagem relativamente aos exames feitos em ambiente hospitalar.

Por outro lado, em alguns doentes a quem foi prescrita esta terapêutica na sequência de, por exemplo, um episódio de exacerbação grave com internamento, a necessidade de oxigenoterapia poderá deixar de se verificar após a convalescença do episódio agudo. A monitorização dos valores da oximetria permitirá, desta forma, levar à suspensão da prescrição, o que constituirá um fator de alívio para o doente, para a família e também para a sociedade, pela redução inerente dos custos.

O conhecimento dos benefícios da atividade física regular em doentes com DPOC, tem levado muitos investigadores a monitorizar a atividade física através do uso de questionários, ou de instrumentos de medida como os pedómetros ou os acelerómetros.

A utilização das novas tecnologias da comunicação aplicadas à saúde, nomeadamente com a Telemedicina, tem permitido encurtar as distâncias entre doentes e profissionais de saúde, bem como o diagnóstico, a orientação e aconselhamento dos doentes e a monitorização clínica à distância [191]. A telemonitorização de doentes com insuficiência respiratória crónica pode traduzir-se em benefícios para a saúde, nomeadamente na redução do número e duração das hospitalizações e na melhoria da qualidade de vida [192].

A monitorização simultânea dos níveis de saturação periférica em oxigénio e da avaliação da duração e intensidade do esforço por um acelerómetro (registo dos equivalentes metabólicos da tarefa ou METs), sendo ambas as informações enviadas por *Bluetooth* para um telemóvel colocado à cintura do doente, poderá ser a solução para uma melhor adequação da oxigenoterapia e avaliação em tempo real do nível de atividade física regular. O objetivo do **Estudo 10** desta tese (Capítulo 4) consistiu na avaliação do valor clínico (*proof of concept*) deste sistema.

2

OBJETIVOS

Capítulo 2

Objetivos

Apesar da intensa investigação desenvolvida no que diz respeito à prevalência, à mortalidade e ao impacto da DPOC, bem como ao papel da reabilitação respiratória em doentes com DPOC, ainda persistem lacunas que importa investigar.

Nesta tese definiram-se como **objetivos gerais** aprofundar o conhecimento da DPOC e suas consequências negativas na mortalidade e morbilidade e clarificar o papel da reabilitação respiratória nos benefícios para a saúde dos doentes com DPOC.

Como **objetivos específicos** procurou-se responder às seguintes questões:

Estudo 1 – Dado que a DPOC é uma doença com um impacto negativo em todo o mundo, pela mortalidade e morbilidade associadas, qual o valor estimado da prevalência em Portugal?

Estudo 2 – Dada a elevada mortalidade em doentes com DPOC avançada que são referenciados para reabilitação respiratória, quais são os fatores preditivos clínicos e funcionais da mortalidade, no período de 3 anos que se segue ao programa de reabilitação respiratória, em doentes seguidos em hospital de dia de insuficientes respiratórios?

Estudo 3 – Dada a perda progressiva da capacidade que os doentes com DPOC apresentam na realização das atividades físicas da vida diária, quais os fatores que melhor permitem identificar o risco destes doentes se tornarem dependentes?

Estudo 4 – Sendo a inflamação sistémica um dos fatores que se associa ao aparecimento das manifestações extrapulmonares da DPOC, como a perda de peso, a disfunção do músculo esquelético, a depressão ou a osteoporose, e a um pior prognóstico com maior número de exacerbações e maior mortalidade, qual é a expressão da inflamação avaliada em repouso e a sua eventual modificação após o

exercício físico? Quais são as características dos doentes que se associam a essa expressão inflamatória?

Estudo 5 – A nova classificação GOLD nas categorias A, B, C e D evidencia melhor a complexidade e a heterogeneidade dos doentes com DPOC. Dado que os componentes agora adicionados à avaliação da obstrução brônquica, nomeadamente os sintomas, o estado geral de saúde e a ocorrência das exacerbações, são potencialmente modificáveis com os programas de RR, quais os resultados na capacidade para o exercício, no controlo da dispneia e no estado geral de saúde, nas diferentes categorias?

Estudo 6 - Sabendo que as comorbilidades são responsáveis pelo agravamento dos sintomas, da qualidade de vida e da capacidade funcional em doentes com DPOC, aumentando o risco de hospitalizações e de mortalidade, qual é a prevalência das comorbilidades na população de doentes que são referenciados para reabilitação respiratória e qual é a sua influência nos resultados dos programas?

Estudo 7 – Sabendo que a intensidade de treino recomendada para que se obtenham benefícios fisiológicos em doentes com DPOC é entre 60 e 80% da potência aeróbica máxima, qual é a intensidade ótima de treino para que se obtenham os melhores resultados centrados no doente – melhoria da capacidade de exercício, dos sintomas e da qualidade de vida?

Estudo 8 – Sabendo que os níveis de atividade física diária nos doentes com DPOC podem ser influenciados por múltiplos fatores e que, por sua vez, a sua diminuição se associa à ocorrência de exacerbações e a maior mortalidade, quais são os principais fatores que influenciam a atividade física na vida diária dos doentes com DPOC? Serão esses fatores potencialmente modificáveis?

Estudo 9 - Sabendo que existe perda dos benefícios obtidos nos programas de RR com treino de exercício caso os doentes não mantenham atividade física regular, qual a evolução da capacidade funcional e do estado de saúde dos doentes com DPOC e insuficiência respiratória crónica, dois anos após completarem um programa de RR?

Estudo 10 – Pressupondo que a atividade física é o fator que melhor prevê a mortalidade global em doentes com DPOC, que esta pode ser avaliada de forma mais rigorosa com o recurso a acelerómetros e cujo incremento pode modificar o prognóstico dos doentes com DPOC, inclusivamente nos insuficientes respiratórios graves cumpridores da oxigenoterapia, conceptualizou-se o sistema TelemOLD. Qual é o valor clínico deste sistema de telemonitorização, que combina a oximetria e a quantificação da atividade física, na capacidade em detetar dessaturação de oxigénio, em melhor adequar a oxigenoterapia de longa duração e em monitorizar a atividade física regular em doentes com DPOC?

3

METODOLOGIA

Capítulo 3

Metodologia

Neste capítulo descreve-se de forma sumária, a metodologia utilizada nos vários estudos, sendo esta detalhada em cada um dos artigos que compõem o capítulo 4.

Estudo 1

- Estudo epidemiológico transversal de base populacional, desenvolvido na área de Lisboa, numa amostra de 600 indivíduos (300 do sexo masculino e 300 do sexo feminino), estratificada por aleatorização simples, em três fases. A estratificação foi iniciada por 8 concelhos suburbanos e 4 concelhos urbanos, seguindo-se uma seleção aleatória de domicílios por amostragem telefónica, e culminando com o convite à participação de indivíduos com pelo menos 40 anos, sendo escolhida em cada domicílio, a pessoa cujo dia de aniversário apresentava o valor mais elevado. Ao aceitar participar, foi então agendada a colheita de dados, mediante a aplicação de questionários e realização de espirometria.

  Para cumprimento do protocolo BOLD foi realizada uma formação de três dias no Kaiser Permanente Center for Health Research em Portland, Oregon, Estados Unidos da América, com a equipa liderada pela Professora Sonia Buist, coordenadora internacional do projeto BOLD, que incluiu a certificação na realização dos estudos funcionais respiratórios e onde se fez a validação dos questionários BOLD para a língua portuguesa.

Estudo 2

- Estudo retrospetivo de coorte histórica de doentes com DPOC seguidos em hospital de dia de insuficiência respiratória entre janeiro de 2008 e dezembro de 2010, após cumprimento de um programa de reabilitação respiratória. Registou-se a taxa de mortalidade observada a um ano, aos dois anos e aos três anos e pesquisaram-se fatores clínicos e funcionais que se associaram à mortalidade.

Estudo 3

- Estudo longitudinal de 6 meses, observacional e de correlação de uma coorte de doentes com DPOC que cumpriram um programa de RR em hospital de dia de insuficiência respiratória, através da aplicação de um questionário de atividades da vida diária e da atribuição de uma graduação de dependência, previamente concebido e validado para a população idosa por uma das autoras deste estudo.

Estudo 4

- Estudo prospetivo de uma coorte de doentes com DPOC referenciados para reabilitação respiratória em que é avaliada a expressão de genes imunorreguladores e inflamatórios sob a forma de ARN mensageiro por transcriptase reversa da reação de polimerase em cadeia, em repouso e a sua variação 1 hora e 24 horas após um teste de exercício com a máxima intensidade tolerada, em tapete rolante ou em bicicleta ergométrica. Foi pesquisada a associação da expressão inflamatória detetada com as caraterísticas clínicas e funcionais dos doentes.

Estudo 5

- Estudo prospetivo de uma coorte de doentes de diferentes categorias A, B, C e D na classificação GOLD, referenciados para RR em ambulatório hospitalar, em que são avaliados antes e após um programa de RR, a capacidade de exercício funcional (distância na prova de marcha de 6 minutos), a capacidade de *endurance*, a dispneia (índice de dispneia de Mahler) e o estado geral de saúde (questionário de doenças respiratórias de *St. George*). O programa incluiu treino de exercício aeróbio em tapete rolante ou em bicicleta, treino de força dos grandes grupos musculares, técnicas de controlo respiratório e de drenagem brônquica, sessões de educação para autogestão e intervenção psicossocial ou nutricional, caso necessário. Foram comparados os resultados da RR entre as diferentes categorias de doentes.

Estudo 6

- Estudo retrospetivo de coorte histórica de doentes com DPOC admitidos num programa de RR na Unidade de Reabilitação Respiratória ao longo de cinco anos em que é avaliada a prevalência de comorbilidades e sua caracterização, bem como a sua influência no protocolo da RR e nos resultados finais dos programas.

Estudo 7

- Estudo prospetivo de equivalência/não inferioridade com aleatorização estratificada em blocos, controlado com grupos paralelos e um rácio de alocação de 1 para 1, desenhado para estudar o efeito de duas intensidades de treino aeróbio a 60 e a 80% da potência aeróbica máxima, nos resultados centrados no doente com DPOC. Os programas de RR desenvolveram-se em 2009 e 2010 na

Unidade de Reabilitação Respiratória, incluíram 20 sessões de treino aeróbico em tapete rolante ou bicicleta ergométrica, treino de força e de flexibilidade e educação para a autogestão. Foram avaliados o estado geral de saúde, a dispneia, as atividades da vida diária, a capacidade de exercício funcional, de *endurance* e máxima.

Estudo 8

- Estudo prospetivo de uma coorte de doentes do sexo masculino com DPOC com limitação moderada a muito grave do fluxo das vias aéreas, seguidos em ambulatório de Pneumologia, em que é avaliada a atividade física pelo número médio de passos registados em pedómetro em três dias consecutivos e pelo questionário de atividades da vida diária do London Chest e depois pesquisada a associação com as caraterísticas clínicas e funcionais.

Estudo 9

- Estudo retrospetivo de uma coorte de doentes com DPOC com limitação grave e muito grave do fluxo das vias aéreas, que realizaram um programa de RR em hospital de dia de insuficiência respiratória e foram seguidos em *follow-up* ao longo de dois anos. Foi avaliada a evolução da capacidade funcional para o exercício através de provas de marcha de seis minutos seriadas, bem como a evolução da qualidade de vida relacionada com a saúde, através da aplicação seriada do questionário de doenças respiratórias de St. George.

Estudo 10

- Estudo prospetivo de uma coorte de doentes com DPOC integrados em programa de RR em hospital de dia de insuficiência respiratória. Foi avaliada a prova de conceito do projeto TelemOLD: qual é o valor clínico deste sistema de telemonitorização, que combina a oximetria e a quantificação da atividade física, na capacidade em detetar dessaturação de oxigénio, em melhor adequar a oxigenoterapia de longa duração e em monitorizar a atividade física regular em doentes com DPOC?

4

ESTUDOS

ESTUDOS 1 a 4

EPIDEMIOLOGIA DA DPOC EM LISBOA, PORTUGAL

MORTALIDADE EM DOENTES COM DPOC AVANÇADA

MORBILIDADE E FUNCIONALIDADE EM DOENTES COM DPOC

INFLAMAÇÃO SISTÉMICA E DPOC – A OBESIDADE TEM UM PAPEL RELEVANTE?

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ORIGINAL ARTICLE

Chronic obstructive pulmonary disease prevalence in Lisbon, Portugal: The burden of obstructive lung disease study☆

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KEYWORDS
COPD prevalence;
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Abstract
Background: There is a great heterogeneity in the prevalence of Chronic Obstructive Pulmonary Disease (COPD) across the world. The Burden of Obstructive Lung Disease (BOLD) initiative was started to measure the prevalence of COPD in a standardized way. We aimed to estimate the prevalence of COPD in Portuguese adults aged 40 years or older of a target population of 2,700,000 in the Lisbon region, in accordance with BOLD protocol.
Methods: A stratified, multi-stage random sampling procedure was used which included 12 districts. The survey included a questionnaire with information on risk factors for COPD and reported respiratory disease and a post-bronchodilator spirometry performed at survey centres.
Results: For the 710 participants with questionnaires and acceptable spirometry, the overall weighted prevalence of GOLD stage I+ COPD was 14.2% (95% C.I. 11.1, 18.1), and stage II+ was 7.3% (95% C.I. 4.7, 11.3). Unweighted prevalence was 20.2% (95% C.I.17.4, 23.3) for stage I+ and 9.5% (95% C.I. 7.6, 11.9) for stage II+. Prevalence of COPD in GOLD stage II+ increased with age and was higher in men. The prevalence of GOLD stage I+ COPD was 9.2% (95% C.I. 5.9, 14.0) in never smokers versus 27.4% (95% C.I. 18.5, 38.5) in those who had smoked ≥20 pack-years. The

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agreement between previous doctor diagnosis and spirometric diagnosis was low, with 86.8% of underdiagnosed individuals.
Conclusions: The 14.2% of COPD estimated prevalence indicates that COPD is a common disease in the Lisbon region. In addition, a large proportion of underdiagnosed disease was detected. The high prevalence of COPD with a high level of underdiagnosis, points to the need of raising awareness of COPD among health professionals, and requires more use of spirometry in the primary care setting.

PALAVRAS-CHAVE
Prevalência da doença pulmonar obstrutiva crónica;
Estudo Burden of Obstructive Lung Disease;
Obstrução das vias aéreas

Prevalência da doença pulmonar obstrutiva crónica em Lisboa, Portugal: estudo burden of obstructive lung disease

Resumo
Introdução: A prevalência da doença pulmonar obstrutiva crónica (DPOC) apresenta valores muito heterogéneos em todo o mundo. A iniciativa *Burden of Obstructive Lung Disease* (BOLD) foi desenvolvida para que a prevalência da DPOC possa ser avaliada com metodologia normalizada. O objetivo deste estudo foi estimar a prevalência da DPOC em adultos com 40 ou mais anos numa população alvo de 2 700 000 habitantes na região de Lisboa, de acordo com o protocolo BOLD.
Métodos: A amostra foi estratificada de forma aleatória multifaseada selecionando-se 12 freguesias. O inquérito compreendia um questionário com informação sobre fatores de risco para a DPOC e doença respiratória autoreportada; adicionalmente, foi efetuada espirometria com prova de broncodilatação.
Resultados: Foram incluídos 710 participantes com questionário e espirometria aceitáveis. A prevalência estimada da DPOC na população no estádio GOLD I+ foi de 14,2% (IC 95%: 11,1; 18,1) e de 7,3% no estádio II+ (IC 95%: 4,7; 11,3). A prevalência não ajustada foi de 20,2% (IC 95%: 17,4; 23,3) no estádio I+ e de 9,5% (IC 95%: 7,6; 11,9) no estádio II+. A prevalência da DPOC no estádio GOLD II+ aumentou com a idade, sendo mais elevada no sexo masculino. A prevalência estimada da DPOC no estádio GOLD I+ foi de 9,2% (IC 95%: 5,9; 14,0) nos não fumadores versus 27,4% (IC 95%: 18,5; 38,5) nos fumadores com carga tabágica de $\geq$ 20 Unidades Maço Ano. Detetou-se uma fraca concordância entre a referência a diagnóstico médico prévio e o diagnóstico espirométrico, com 86,8% de subdiagnósticos.
Conclusões: O achado de uma prevalência estimada da DPOC de 14,2% sugere que esta é uma doença comum na região de Lisboa, contudo com uma elevada proporção de subdiagnósticos. Estes dados apontam para a necessidade de aumentar o grau de conhecimento dos profissionais de saúde sobre a DPOC, bem como a necessidade de maior utilização da espirometria nos cuidados de saúde primários.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) was the sixth-most common cause of death worldwide in 1990, but is projected to become the third-most common cause by the year 2030[1]; it is already ranked fourth in developed countries,[2–5] with approximately 2.75 million deaths per year, or 4.8% of all deaths.[3]

The prevalence of COPD in the general population across all ages rises steeply to above 10% amongst people who are aged over 40. The prevalence increases considerably with age.[2]

In Portugal, the previously reported prevalence was 5.34%,[6] based on a study of 2002. However, this study had some methodological limitations related not only to the age range of the individuals studied (35–69 years old), but also to the criteria used for airway obstruction definition (pre-bronchodilator fixed ratio criteria) due to the absence of a bronchodilator test. In fact, epidemiological studies should not exclude older individuals because life expectancy in Portugal, is higher than 70 years old (respectively 76 and 82 years for males and females).[7]

COPD prevalence across the world varies considerably, due to differences in methodologies, sampling and diagnostic criteria for COPD, and also to differences in patterns of cigarette smoking.

Accurate prevalence studies are needed to guide future projections of the burden of this disease in each country, and to assist public health officials in the planning to meet the growing demand for health care resources.[8]

The Burden of Obstructive Lung Disease (BOLD) Initiative developed standardized methods for estimating of COPD prevalence. These methods can be used in countries at all levels of development to measure the worldwide prevalence of COPD and its risk factors in adults aged 40 years and older, and to investigate variation in prevalence across countries

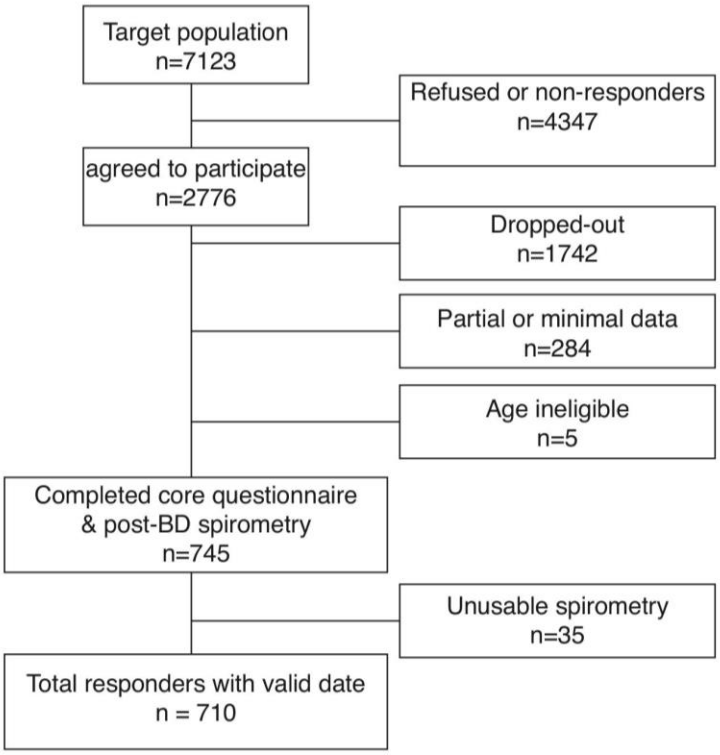

Figure 1 Sampling of participants' final sample.

by age, gender, and smoking status.[8] Overall 20 countries have completed their study participation and other sites are in progress.[9]

The aim of our study was to estimate the prevalence of COPD based on a representative sample of non-institutionalized adults aged 40 years and over, carried out in Lisbon, Portugal, using standardized post-bronchodilator (post-BD) spirometry, as per the BOLD protocols.

Material and methods

We conducted a cross-sectional population survey following BOLD protocol, as described in detail elsewhere.[10] Study fieldworkers were trained and certified in study methodology.

Sample size

A minimum sample size of 600 individuals was considered to provide an acceptable level of precision for prevalence estimates, assuming simple random sampling.[10]

Study population

The survey was conducted among the residents of Lisbon region, whose population represents nearly 27% of the total Portuguese inhabitants, according to the 2007 census. The survey area was divided into two broad zones which are distinct regarding the demographic structure, socio-economic status, population density and environmental stress: the inner city zone, with about 800,000 residents, and the suburbs with about 1,900,000 residents.

We used a stratified, multi-stage random sampling procedure. In the first sampling stage, 8 suburban and 4 inner-city districts were randomly selected from a total of 173 suburban and 53 inner-city districts of Lisbon. In the second sampling stage, households from the selected districts were randomly selected using a phone list that covered over 90% of the inhabitants of the districts selected. In the third sampling stage, individuals from the households selected were invited to participate if they were aged 40+. There was also a Minimal Data/Refusal questionnaire for participants who were not willing to participate in the full protocol (non responders). A professional survey-specialized phone-call centre was contracted to make contacts and invite participation. Data were collected between 16th of June and 7th of November 2008.

Of the 7123 individuals, whom we attempted to contact, 2776 agreed (over the phone) to take part in the survey. From those, 745 (27%) completed the protocol (core questionnaire plus post-BD spirometry), but 35 participants did not meet the American Thoracic Society (ATS) spirometry quality control criteria. Therefore, 710 responders (331 men and 379 women) constituted the final sample for this analysis (Fig. 1).

Written informed consent was obtained from each participant and ethics approval was granted by Ethics Committee

of Hospital Pulido Valente and by the Portuguese Data Protection Authority.

Spirometry

At survey centres located in each county, pre and post-BD spirometry tests were performed according to the ATS guidelines[11] by trained and certified technicians using the nddEasyOne™ Spirometer (ndd Medizintechnik; Zurich, Switzerland). At least three technically acceptable manoeuvres were performed, in a seated position, to obtain a minimum of two reproducible spirometry tests, with variability less than 200 mL, for both the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). Two puffs of salbutamol (200 μg) were administered with a metered dose inhaler connected to a spacer (15 cm length/2.1 cm diameter) and 20 min later the test (post-BD spirometry) was repeated. Spirometry tests were defined as acceptable, if they were free from artefacts, sudden stops, and back-extrapolated volumes greater than 5.0% of FVC or 150 mL, whichever was greater.[11]

Spirometry data were sent electronically to the Pulmonary Function Quality Control Centre (Co-ordinating Centre in UK) where each spirometry was reviewed and graded according to its quality, based on criteria from the BOLD project.[11] Study technicians were continuously monitored and if a technician's quality-score dropped below a pre-set level, he/she had to stop testing and be re-trained and re-certified.

Questionnaire data

All participants answered BOLD questionnaires with demographic and clinical data, including doctor-diagnosed respiratory conditions.[10]

The original BOLD questionnaires were translated from English to Portuguese and then back-translated to assure accuracy and conceptual equivalence. Questionnaires were obtained by face-to-face interview with trained and certified staff. A core questionnaire was completed for all individuals considered as responders. A minimal data/refusal questionnaire was collected from the non-responders group. Non-responders were eligible individuals who missed the core questionnaire and/or post-BD spirometry. By contrast responders completed both items. All the questionnaires were revised for completeness, accuracy and consistency within 48 hours of the interview by a team of seven certified physicians. All data were sent and quality controlled by the BOLD Co-ordinating Centre in UK.

Definitions

COPD was defined based on post-BD spirometry. In accordance with the Global Initiative for COPD (GOLD) guidelines,[12] a not fully reversible airway obstruction was defined, as a post-BD $FEV_1/FVC < 0.7$. This definition was also used for COPD stage I+ in the analysis. Severity of COPD was defined as stage II+ if post-BD $FEV_1 < 80\%$ predicted, as stage III+ if post-BD $FEV_1 < 50\%$ predicted and stage IV if post-BD $FEV_1 < 30\%$. Percent predicted values[13] for Caucasian men and women were calculated using the National Health and Nutrition Examination Survey (NHANES) III reference equations.[13]

COPD diagnosis was considered based on the post-BD lung function criteria without requiring the presence of symptoms or documented exposure to a known causative agent, as per BOLD protocol.[8–10]

COPD doctor's diagnosis (dx) was defined as the self-reported physician's diagnosis of emphysema, chronic bronchitis or COPD.

Subjects were classified as current smokers, ever smokers or never smokers. Ever-smokers (including former and current smokers) were defined as individuals who smoke more than 20 packs of cigarettes in a lifetime or more than 1 cigarette per day during one year. The number of pack-years of cigarette smoking was defined as the average number of cigarettes smoked per day divided by 20 (i.e. packs per day) times the duration of smoking in years. Because of the low occurrence of stage IV COPD in the population samples, stages III and IV were combined in this paper.

Statistical analysis

This analysis included 710 Portuguese participants who completed the core questionnaire and who had acceptable post-BD spirometry measures. Results are presented stratified by gender, age-groups, pack-years smoked and as totals.

Prevalence estimates were calculated for the overall Lisbon population, as well as for subgroups defined by gender and either age or pack-years of cigarette smoking. Because the distribution of participants in the responders' data differed slightly from that for Lisbon population, the data were weighted according to age and gender group, so that there would be a better match of the resulting prevalence estimates with those of Lisbon as a whole. In the weighting process each subject had a weight attached to him, where the weight corresponds to the number of people this subject represents in the population. The weighting was used in order to overcome limitations of sample survey, such as differential non-response rates, or under coverage of some sub-populations.

Weighted population-based estimates of COPD prevalence and their respective 95% confidence intervals (C.I.) were computed using survey data methods in STATA (STATA Corporation, College Station, TX, USA). These calculations were made to assure that the estimated prevalence and the respective 95% C.I. properly reflected the sampling design.

Results

Table 1 shows that there were no differences between responders and non-responders who completed minimal data questionnaire, except for gender, where non-responders were predominantly male.

Table 2 summarizes the main characteristics of the participants' final sample. More than half of the subjects (63.0%) were 60 years or older and 53.4% were female. Current or former smoking was more frequent in men,

Table 1 Comparison of responders and non-responders for BOLD Portugal.*

	Responders[a]	Non-responders[b]	*p*-Value[c]
Age	*N* = 745	*N* = 2026	
40–49	99 (13%)	252 (12%)	.89
50–59	174 (23%)	473 (23%)	
60–69	217 (29%)	581 (29%)	
70+	255 (34%)	720 (36%)	
Gender	*N* = 745	*N* = 2030	
Male	349 (47%)	1086 (53%)	.002
Female	396 (53%)	944 (47%)	
Smoking status	*N* = 745	*N* = 283	
Current	99 (13%)	30 (11%)	.18
Former	197 (26%)	65 (23%)	
Never	449 (60%)	188 (66%)	
Doctor previous diagnosed asthma, emphysema, CB or COPD	*N* = 743	*N* = 283	
Yes	113 (15%)	33 (12%)	.15
No	630 (85%)	250 (88%)	
Other co-morbid conditions	*N* = 745	*N* = 283	
Yes	397 (53%)	159 (56%)	.41
No	348 (47%)	124 (44%)	

* Values are given as No. (%).
[a] Responders are those who completed post-BD spirometry and the core questionnaire.
[b] Non-responders are eligible individuals who are missing the core questionnaire and/or post-BD spirometry, but for whom the tabulated variable is known.
[c] Two-sided *p*-value based on Pearson chi-square test.

Table 2 Characteristics of the study sample.*

Characteristics	Male	Female	Total
Gender	331 (47%)	379 (53%)	710 (100%)
Age, yr			
40–49	35 (11%)	61 (16%)	96 (14%)
50–59	74 (22%)	93 (25%)	167 (24%)
60–69	114 (34%)	91 (24%)	205 (29%)
70+	108 (33%)	134 (35%)	242 (34%)
Smoking status			
Current	52 (16%)	42 (11%)	94 (13%)
Former	149 (45%)	41 (11%)	190 (27%)
Never	130 (39%)	296 (78%)	426 (60%)
Symptoms			
Chronic cough	20 (6%)	54 (14%)	74 (11%)
Chronic phlegm	38 (11%)	55 (15%)	93 (13%)
Wheezing	86 (26%)	111 (29%)	197 (28%)
Dyspnoea	51 (18%)	85 (29%)	136 (24%)
Doctor diagnosed asthma, emphysema, chronic bronchitis or COPD	48 (15%)	60 (16%)	108 (15%)
Doctor diagnosed asthma	35 (11%)	47 (12%)	82 (12%)
Doctor diagnosed COPD	2 (1%)	2 (1%)	4 (1%)
Other co-morbid conditions	182 (55%)	192 (51%)	374 (53%)

* Values are given as No. (%).

Table 3 Estimated-population prevalence of smoking habits by age and gender.*

	40–49 yr	50–59 yr	60–69 yr	70+ yr	Total
Male					
Current smokers	27.1 (20.6, 34.9)	29.5 (12.8, 54.3)	15.5 (8.3, 27.0)	11.0 (3.8, 28.1)	22.1 (13.5, 34.1)
Ever smokers	57.7 (34.5, 77.9)	67.6 (49.7, 81.4)	53.0 (40.4, 65.3)	64.4 (50.5, 76.2)	60.7 (54.3, 66.7)
Never smokers	42.3 (22.1, 65.5)	32.4 (18.5, 50.3)	47.0 (34.7, 59.6)	35.6 (23.8, 49.5)	39.3 (33.3, 45.7)
Female					
Current smokers	33.1 (21.0, 48.0)	12.3 (7.3, 19.9)	7.0 (2.7, 16.7)	3.0 (1.0, 8.6)	14.4 (10.0, 20.3)
Ever smokers	51.0 (34.4, 67.3)	25.1 (13.1, 42.6)	21.6 (15.4, 29.4)	13.5 (5.9, 27.9)	28.3 (21.3, 36.6)
Never smokers	49.0 (32.7, 65.6)	75.9 (57.4, 86.9)	78.4 (70.6, 84.6)	86.5 (72.1, 94.1)	71.7 (63.4, 78.7)
Total					
Current smokers	30.2 (21.4, 40.9)	20.4 (12.9, 30.7)	10.9 (6.8, 17.1)	6.0 (3.1, 11.5)	17.9 (12.5, 25.0)
Ever smokers	54.2 (40.7, 67.0)	45.1 (37.1, 53.5)	36.0 (30.2, 42.2)	32.8 (24.5, 42.3)	42.9 (36.6, 49.4)
Never smokers	45.8 (33.0, 59.3)	54.9 (46.5, 62.9)	64.0 (57.8, 69.8)	67.2 (57.7, 75.5)	57.1 (50.6, 63.4)

* Weighted population estimate, with 95% confidence interval shown in parenthesis. Un-weighted data for the sample of responders are shown in the electronic appendix.

while never smoking was more prevalent in women. Table 3 presents weighted population estimate of smoking habits by age and gender (unweighted data are shown in Table 3a of the electronic appendix). The prevalence of total current smokers was 17.9% (95% C.I. 12.5, 25.0). The highest current smoking prevalence occurred in the female 40–49 year age-group (33.1%, 95% C.I. 21.0, 48.0), decreasing with age. Among men, the highest prevalence was in the 50–59 year age-group. Ever smoking showed the highest prevalence in men aged 70+ years old.

Table 4a (electronic appendix) shows the unweighted estimated prevalence of COPD by gender and pack years as 20.2% (95% C.I. 17.4, 23.3) and 9.5% (95% C.I. 7.6, 11.9) respectively for COPD stage I+ and II+. Overall, the weighted estimated-population prevalence for GOLD stage I+ COPD was 14.2% (95% C.I. 11.1, 18.1), 18.7% (95% C.I. 12.6, 26.8) for males and 10.5% (95% C.I. 7.5, 14.7) for females (Table 4). In individuals reporting respiratory symptoms the estimated population prevalence for GOLD stage I+ COPD was higher, respectively 19.9% (95% C.I. 8.7, 39.3) for chronic cough, 21.7% (95% C.I. 13.1, 33.7) for chronic phlegm, 23% (95% C.I. 17.3, 29.8) for wheezing and 22.7% (95% C.I. 11.5, 39.9) for dyspnoea (data not shown). Concerning GOLD stage II+ COPD the estimated prevalence was 7.3% (95% C.I. 4.7, 11.3), and 1.4% (95% C.I. 0.23, 2.47) for GOLD stage III+, with higher levels in older people (70+ years: 5%); it was absent in the age group 40–49 years (Figs. 2 and 3).

According to Table 4, the population-estimated prevalence of GOLD stage I+ COPD was 9.2% (95% C.I. 5.9, 14.0) in participants who had never smoked and increased with the number of pack-years; it was 27.4% (95% C.I. 18.5, 38.5) in those with a smoking history of ≥20 pack-years. Similarly, the population-estimated prevalence of GOLD stage II+ COPD

Table 4 Estimated-population prevalence of COPD according to GOLD stage I+, GOLD stage II+ and doctor's previous diagnosis by gender and pack-years.*

	Never smokers %	0–10 pack-yr %	10–20 pack-yr %	20+ pack-yr %	Total %
GOLD stage I+					
Male	11.2 (5.5, 21.5)	19.8 (6.8, 45.4)	8.6 (2.2, 28.1)	27.9 (20.4, 40.0)	18.7 (12.6, 26.8)
Female	8.2 (4.5, 12.2)	5.0 (0.9, 22.9)	22.6 (6.3, 55.7)	26.0 (8.1, 58.3)	10.5 (7.5, 14.7)
Total	9.2 (5.9, 14.0)	11.5 (4.7, 25.4)	13.4 (6.4, 26.0)	27.4 (18.5, 38.5)	14.2 (11.1, 18.1)
GOLD stage II+					
Male	3.7 (1.4, 9.6)	3.6 (0.7, 17.0)	3.3 (0.5, 18.1)	17.2 (8.6, 31.5)	9.1 (4.4, 17.7)
Female	4.6 (2.7, 7.6)	3.3 (0.7, 14.6)	22.6 (6.3, 55.7)	10.4 (3.5, 27.2)	5.8 (3.8, 8.8)
Total	4.3 (2.6, 7.1)	3.4 (1.3, 8.6)	9.9 (3.4, 25.4)	15.4 (7.9, 27.8)	7.3 (4.7, 11.3)
Doctor's previous diagnosis					
Male	1.3 (0.4, 4.3)	3.5 (0.4, 23.2)	21.3 (5.0, 58.2)	9.8 (5.1, 18.1)	6.8 (3.8, 11.8)
Female	5.0 (3.1, 8.1)	8.4 (3.6, 18.3)	10.9 (3.1, 32.2)	6.0 (1.6, 20.3)	5.8 (4.4, 7.6)
Total	3.9 (2.2, 6.7)	6.2 (2.4, 15.0)	17.1 (4.8, 45.7)	8.8 (5.9, 12.9)	6.3 (4.7, 8.3)

* Weighted population estimate, with 95% confidence interval in parenthesis. Un-weighted data for the sample of responders, are shown in the electronic appendix.

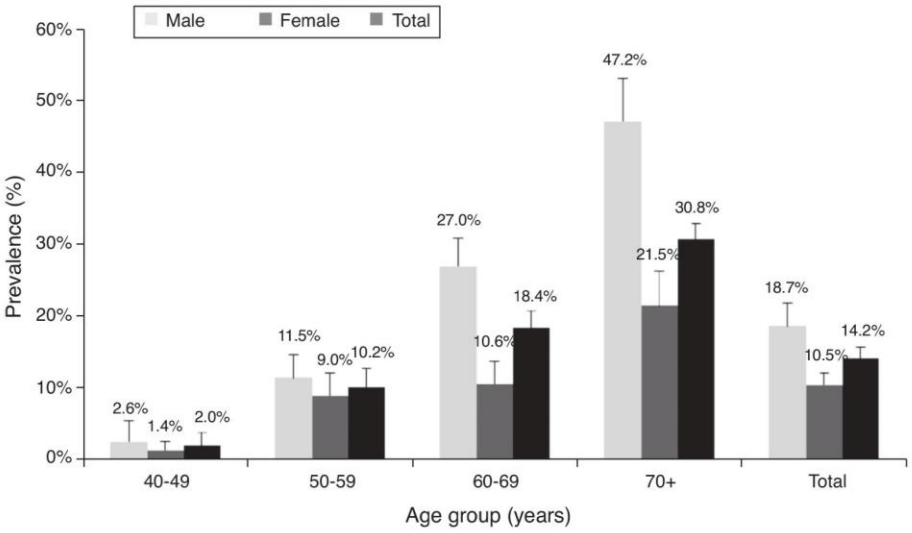

Figure 2 Prevalence of GOLD stage I+ COPD by age group and gender.

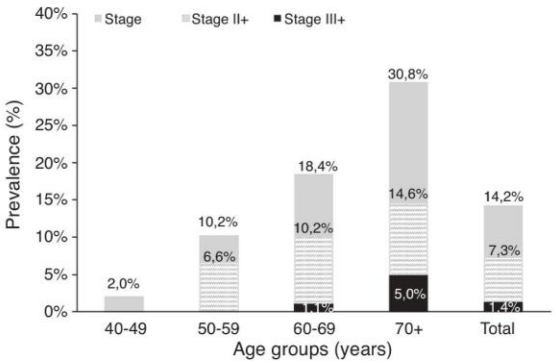

Figure 3 Estimated prevalence of COPD by age and severity.

was 4.3% (95% C.I. 2.6, 7.1) in never smokers and 15.4% (95% C.I. 7.9, 27.8) in participants with ≥20 pack-year's smoking history.

Overall, the population-estimated prevalence of reported COPD doctor's diagnosis was much lower than COPD spirometrically defined (6.3% versus 14.2%). The prevalence of COPD doctor's dx was not associated with an increase of pack years of smoking (Table 4).

From the total group with COPD spirometric diagnosis, 86.8% did not report previous COPD doctor's dx (underdiagnosis). On the other hand, from the total group that reported previous COPD doctor's dx, 61.2% were not confirmed by spirometric analysis (overdiagnosis).

Discussion

The main finding of our study is that COPD is a highly prevalent disease in Lisbon-Portugal, with an estimated prevalence of 14.2% in adults, aged 40 years or older. The overall prevalence of GOLD-defined COPD was higher in men than in women. COPD prevalence increased with age and smoking habits, with the highest estimated prevalence in men (47.2%) 70+ years old. Our data also support a high level of underdiagnosis (86.8%) and an unexpected high prevalence (9.2%) in never smokers.

It is necessary to quantify COPD prevalence, so as to document the effects of COPD effects on disability, quality of life and health care costs, and also to inform governments and public health authorities in planning to meet the growing demand for services.[8,10] The BOLD initiative was developed standardized methods for estimating COPD prevalence and for obtaining data about risk factors. The first BOLD report of COPD prevalence across the world showed heterogeneity between countries and genders. Moreover, the reported prevalence tended to be greater than those previously known.[8]

The Lisbon BOLD survey is the first Portuguese study about COPD prevalence with a standardized methodology implemented internationally allowing comparison across countries. The main strength of this survey was the use of BOLD protocol, with a rigorous methodology to achieve the maximum accuracy and completeness of the survey and a high-quality post-BD spirometry. This methodology ensured that data were as easy to compare as possible with other BOLD studies.[10]

The reported low response rate (27%) of our study was one of the main limitations; this can be justified as a reactive attitude of participants to the high number of calls made by marketing companies in Portugal. Nevertheless, our response rate was similar to other published data sites (Vancouver and Kentucky),[8] which also used random-digit-dialling.

In order to make sure that the studied sample was representative of the whole target population, a minimal data questionnaire was collected from the non responders, making it possible to compare both groups (responders/non

responders). Except for gender, there were no differences between the groups in relation to age, risk factors and clinical profile. To deal with the high non-response rate and also gender differences, more telephone contacts were made to obtain data from at least 300 females and 300 males. In addition, in order to overcome the potential for response bias, we used weighting for the adjustment of prevalence to the target population.[10]

Before the BOLD results became available, Portuguese official prevalence of COPD was 5.34%, based on a study from 2002.[6] Portugal Lisbon BOLD data revealed a higher value of COPD prevalence (14.2%). So far, all the projections and health planning regarding COPD have been based on the previous prevalence figures meaning that the real burden of COPD has been underestimated.

Because the two studies used different methodologies, their results should not be compared.[14] Regarding the 2002 study, there were some methodological issues that make comparison impracticable. In fact, this study used a different source population, a restrictive sample in relation to age range and also different COPD diagnosis criteria (without post-BD spirometry) and reference equations.

Comparing our data to the international BOLD studies we conclude that Portuguese COPD prevalence is lower than many countries prevalence,[2,8,16–19] although similar to the prevalence of some European countries like Germany (13.2%)[20] and Sweden (16.2%).[21] These differences could be attributed to different levels of smoking in the population, or possibly other risk factors, which are not analyzed here and might need further investigation (e.g. occupation, biomass, air pollution).

In our study, NHANES III equations were used to estimate the prevalence of COPD Stage II+, in order to allow comparisons between countries. However it should be noted that the choice of the right setting of predicted equations is a matter of debate and might influence prevalence estimates.

Our data showed that COPD prevalence increases with age, being higher above 70 years old. It is worth noting that, with ageing, the prevalence in men becomes twice the prevalence in women of the same age group, probably reflecting ever smoking prevalence that corresponds to the cumulative effect of tobacco. Taking into account that COPD stage I+ is defined by the fixed ratio FEV_1/FVC, and that this ratio falls with age in healthy individuals,[22] the high prevalence found in older people could also represent overdiagnosis (47.2% in stage I+ versus 17.2% in stage II+). Nevertheless, we still found the same tendency for age related increase in COPD prevalence in stage II+, although less pronounced.

In the group of females with 10–20 pack-yr the prevalence is exactly the same for GOLD stage COPD I+ and II+ (Table 4), meaning that, in our sample, there were no women in the group with a FEV1/FVC < 70% and FEV1 > 80% predicted. Although unusual, this data was double-checked and confirmed.

As found in other studies,[8,15,18–20] there was also a positive trend with the increasing of pack-years, confirming smoking as an important risk factor for the development of the disease.[12] In fact, above 20 pack-years COPD prevalence doubles (27.4% versus 14.2%), representing an even higher burden of healthcare resources utilization and costs.[23]

Another important issue of this study was the estimate of 17.9% for the prevalence of current smoking in Portuguese people older than 40 years old. This data is consistent with the official prevalence data (17.2%) from the National Health survey of 2005/2006.[24] The highest prevalence of smoking habits found in younger women (40–49 years) strengthens the future projection of an increase of COPD in women, and also the need to target teenagers and young women in smoking cessation campaigns. Concerning never smokers, an unexpected COPD prevalence of 9.2% was found, suggesting a possible overdiagnosis by spirometric parameters. Nevertheless, the COPD prevalence of 4.3% for stage II+, could be the expression of other risk factors that should also be investigated (e.g. biomass exposure, childhood respiratory tract infections, past tuberculosis). Moreover in some people, this high prevalence might indicate asthma with remodelling in the small airways.[8] Similar findings have been described in other countries.[5]

The finding of higher levels of COPD prevalence in symptomatic subjects than in the general population was also expected[12] and the need for a spirometry should be brought to the attention of primary care physicians.

In this study, a gap was found between the presence of airflow obstruction defined by GOLD criteria and doctor's diagnosis. Overall, only 6.3% of the participants reported COPD doctor's diagnosis, while GOLD stage I+ registered 14.2%. Moreover, the difference is even greater if we base our analysis on the degree of concordance between COPD doctor diagnosis and spirometric diagnosis. In fact, only 13.2% of spirometrically diagnosed COPD had been previously diagnosed (underdiagnosis). These data are consistent with those of Spain where, despite an eventual decrease in COPD prevalence, there are still high levels of underdiagnosis.[25–27] Furthermore, 61.2% of the reported cases of ''COPD'' declared by the participants to have been ''doctor diagnosed'' were not confirmed by spirometry (overdiagnosis). These numbers clearly show a high degree of COPD misdiagnosis and highlight the urgency to improve physicians' knowledge about COPD diagnosis, and the need to emphasize the use of spirometry, particularly with symptomatic subjects.

Conclusions

The 14.2% estimated-prevalence indicates that COPD is a common disease in the Lisbon region. The high prevalence of COPD with a large proportion of undiagnosed disease, highlights the importance of raising awareness of COPD among health professionals, and requires more use of spirometry in the primary care setting. Despite ageing and smoking remain major risk factors for COPD, other risk factors contributing to the presence of disease in never smokers should be investigated in future studies.

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Conflicts of interest

The BOLD project in Portugal was conducted by the Respiratory Portuguese Society to the Co-ordinating Centre located at the Imperial College, UK and funded by Boehringer Ingelheim and Pfizer.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rppneu.2012.11.004.

References

1. World Health Organization. World Health Statistics 2008 [Internet]. June 2009. Available in: http://www.who.int/whosis/whostat/2008/en/index.html [aforementioned June 2011].
2. Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ, et al. Epidemiology and costs of chronic obstructive pulmonary disease. Eur Respir J. 2006;27:188–207.
3. Raherison C, Girodet PO. Epidemiology of COPD. Eur Respir Rev. 2009;18:213–21.
4. Schirnhofer L, Lamprecht B, Vollmer WM, Allison MJ, Studnicka M, Jensen RL, et al. COPD prevalence in Salzburg, Austria: results from the burden of obstructive lung disease (BOLD) study. Chest. 2007;131:29–36.
5. Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, et al. COPD in never-smokers: results from the population-based burden of obstructive lung disease study. Chest. 2011;139:752–63.
6. Cardoso J, Reis Ferreira J, Almeida J, Santos JM, Rodrigues F, Matos MJ. Prevalence of Chronic Obstructive Pulmonary Disease (COPD) in Portugal. Am J Respir Crit Care Med. 2003:A110.
7. Instituto Nacional de Estatística. Dados para 2008–2010. Available from: www.ine.pt/portal [accessed 15.02.11].
8. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al., BOLD Collaborative Research Group. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007;370:741–50.
9. Burden of Lung Disease Initiative (BOLD) [Internet]. Available from: http://www.boldstudy.org/; 2011 [aforementioned April 2011].
10. Buist AS, Vollmer WM, Sullivan SD, Weiss KB, Lee TA, Menezes AM, et al. The Burden of Obstructive Lung Disease Initiative (BOLD): rationale and design. COPD. 2005;2:277–83.
11. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med. 1995;152:1107–36.
12. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al., Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176:532–55.
13. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159:179–87.
14. Cerveri I, de Marco R. What makes large epidemiological studies comparable? Eur Respir J. 2010;36:720–1.
15. Menezes AM, Perez-Padilla R, Jardim JR, Muiño A, Lopez MV, Valdivia G, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet. 2005;366:1875–81.
16. Methvin JN, Mannino DM, Casey BR. COPD prevalence in southeastern Kentucky: the burden of lung disease study. Chest. 2009;135:102–7.
17. Idolor LF, de Guia TS, Francisco NA, Roa CC, Ayuyao FG, Tady CZ, et al. Burden of obstructive lung disease in a rural setting in the Philippines. Respirology. 2011;16:1111–8.
18. Benediktsdóttir B, Gudmundsson G, Jörundsdóttir KB, Vollmer W, Gíslason T. Prevalence of COPD in Iceland – the BOLD study. Laeknabladid. 2007;93:471–7.
19. Geldmacher H, Biller H, Herbst A, Urbanski K, Allison M, Buist AS, et al. The prevalence of chronic obstructive pulmonary disease (COPD) in Germany. Results of the BOLD study. Dtsch Med Wochenschr. 2008;133:2609–14.
20. Vanfleteren LE, Franssen FM, Wesseling G, Wouters EF. The prevalence of chronic obstructive pulmonary disease in Maastricht, the Netherlands. Respir Med. 2012;106:871–4.
21. Danielsson P, Ólafsdóttir IS, Benediktsdóttir B, Gíslason T, Janson C. The prevalence of chronic obstructive pulmonary disease in Uppsala, Sweden – the Burden of Obstructive Lung Disease (BOLD) study: cross-sectional population-based study. Clin Respir J. 2012;6:120–7.
22. Vollmer WM, Gíslason T, Burney P, Enright PL, Gulsvik A, Kocabas A, et al. Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. Eur Respir J. 2009;34:588–97.
23. Llor C. Prevalence and impact of undiagnosed chronic obstructive pulmonary disease. Hot Topics Respir Med. 2010;5:9–12.
24. Instituto Nacional de Estatística e Instituto Nacional de Saúde Dr. Ricardo Jorge. Inquérito Nacional Saúde 2005/2006; p. 253.

25. Peña VS, Miravitlles M, Gabriel R, Jiménez-Ruiz CA, Villasante C, Masa JF, et al. Geographical variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest. 2000;118:981–9.
26. Miravitlles M, Soriano JB, García-Río F, Muñoz L, Duran-Tauleria E, Sanchez G, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. Thorax. 2009;64:863–8.
27. Soriano JB, Ancochea J, Miravitlles M, García-Río F, Duran-Tauleria E, Muñoz L, et al. Recent trends in COPD prevalence in Spain: a repeated cross-sectional survey 1997–2007. Eur Respir J. 2010;36:758–65.

Appendix. Supplementary material

Table 1a – Prevalence of smoking habits in the studied sample by age and gender*

	40-49 yr	50-59 yr	60-69 yr	70+ yr	Total
Male					
Current smokers	27.8 (15.6, 44.4)	23.4 (15.3, 34.1)	14.4 (9.1, 22.0)	8.5 (4.6, 15.0)	15.8 (12.3, 20.0)
Ever smokers	63.9 (47.3, 77.7)	63.6 (52.4, 73.6)	56.8 (47.7, 65.4)	60.2 (51.1, 68.6)	60.2 (54.9, 65.2)
Never smokers	36.1 (22.3, 52.7)	36.4 (26.4, 47.6)	43.2 (34.6, 52.3)	39.8 (31.4, 48.9)	39.8 (34.8, 45.1)
Female					
Current smokers	33.3 (22.8, 45.8)	13.4 (7.9, 45.8)	7.1 (3.4, 14.1)	2.2 (0.7, 6.6)	11.1 (8.4, 14.6)
Ever smokers	49.2 (37.2, 61.4)	23.7 (16.3, 33.2)	19.2 (12.6, 28.1)	9.5 (5.6, 15.7)	21.7 (17.9, 65.2)
Never smokers	50.8 (38.6, 62.8)	76.3 (66.8, 83.7)	80.8 (71.9, 87.4)	90.5 (84.3, 94.4)	78.3 (73.9, 82.1)
Total					
Current smokers	31.3 (23.0, 41.1)	17.8 (12.8, 24.2)	11.1 (7.5, 16.0)	5.1 (3.0, 8.6)	13.3 (11.0, 15.9)
Ever smokers	54.5 (44.7, 64.1)	41.4 (34.3, 48.8)	39.6 (33.3, 46.3)	32.9 (27.4, 38.9)	39.7 (36.3, 43.3)
Never smokers	45.5 (35.9, 55.3)	58.6 (51.2, 65.7)	60.4 (53.7, 66.7)	67.1 (61.1, 72.6)	60.3 (56.7, 63.7)

*Un-weighted data for the sample of responders, with 95% confidence interval shown in parenthesis

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Table 2a –Prevalence of COPD, in the studied sample, according to GOLD stage I+, GOLD stage II+ and doctor's previous diagnosis by gender and pack-years*

	Never smokers %	0-10 pack-yr %	10-20 pack-yr %	20+ pack-yr %	Total %
GOLD stage I+					
Male	18.3 (12.6, 25.9)	26.8 (15.5, 42.3)	23.1 (10.8, 42.8)	38.8 (30.9, 47.3)	27.9 (23.4, 33.0)
Female	9.4 (3.1, 16.4)	9.4 (3.1, 25.4)	18.8 (6.2, 44.7)	25.0 (13.6, 41.5)	13.4 (10.3, 17.2)
Total	14.1 (11.1, 17.7)	19.2 (11.7, 29.8)	21.4 (11.5, 36.3)	35.9 (29.0, 43.4)	20.2 (17.4, 23.3)
GOLD stage II+					
Male	6.1 (3.1, 11.7)	4.9 (1.2, 17.5)	7.8 (1.9, 26.1)	20.1 (14.2, 27.8)	11.7 (8.7, 15.6)
Female	6.8 (4.4, 10.2)	6.3 (1.6, 21.8)	18.8 (6.2, 44.7)	11.1 (4.2, 26.1)	7.6 (5.3, 10.7)
Total	6.6 (4.6, 9.3)	5.5 (2.1, 13.7)	11.9 (5.0, 25.6)	18.2 (13.1, 24.8)	9.5 (7.6, 11.9)
Doctor's previous diagnosis					
Male	2.2 (0.7, 6.5)	2.4 (0.3, 15.1)	7.1 (1.8, 24.5)	10.7 (6.6, 17.0)	6.0 (4.0, 9.1)
Female	5.5 (3.4, 8.7)	15.6 (6.7, 32.5)	11.8 (3.0, 36.8)	7.9 (2.6, 21.8)	6.8 (4.7, 9.8)
Total	4.5 (2.9, 6.8)	8.1 (3.7, 16.9)	8.9 (3.4, 21.4)	10.1 (6.5, 15.5)	6.5 (4.9, 8.5)

*Un-weighted data for the sample of responders, with 95% confidence interval shown in parenthesis

2

MORTALITY PREDICTIVE FACTORS IN SUBJECTS WITH COPD AFTER A PULMONARY REHABILITATION PROGRAM – A 3 YEARS STUDY

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Abstract

Background:

COPD is a high mortality disease and projected to become the third worldwide cause of death by 2030.

Our aim was to evaluate predictors of 3 years' mortality and factors associated with early (1 year) and late (second and third year) mortality in subjects with severe COPD that completed a pulmonary rehabilitation program (PRP).

Methods:

A historical cohort study was performed on COPD subjects admitted to respiratory failure daily-hospital unit for PRP, from January 2008 to December 2010.

Population was characterized based on sociodemographic factors, body mass index, smoking habits, lung function tests, respiratory failure, comorbidities, bacterial colonization, modified Medical Research Council (mMRC) dyspnea index, 6-minute walking test (6MWT), mechanical ventilation, non-invasive ventilation, long term oxygen therapy, hospital admissions and mortality.

Results:

From 183 subjects that completed a PRP, 93 had COPD. Our cohort had 78 male and 15 female subjects. The mean age was 68.6 (SD=8.8) years, ranging from 43 to 85 years. After PRP, there were fewer, although not statistically different hospital admissions (2.1 *versus* 1.7; P = .17). Three years after PRP, 34 subjects died (36.6%). Hypercapnic respiratory failure (P = .02), non-invasive ventilation (P = .002), lung cancer (P = .001), shorter 6MWD (P = .03) and higher number of previous hospital admissions (P < .001) were associated with a higher mortality rate.

Conclusion:

There is a high mortality rate in late stage patients with COPD. The most relevant factors associated with mortality were lung cancer, respiratory failure and non-invasive ventilation, severe exacerbations with hospitalization and lower functional exercise capacity.

Key words

COPD, pulmonary rehabilitation, mortality, functional exercise capacity, lung cancer, respiratory failure, non-invasive ventilation, exacerbations

Abbreviation List

PR: Pulmonary Rehabilitation

PRP: Pulmonary Rehabilitation Program

mMRC: modified Medical Research Council

6MWT: 6-minute walking test

6MWD: 6-minute walking distance

GOLD: Global Initiative for Chronic Obstructive Lung Disease

TLC: Total lung capacity

RV: Residual volume

DLCOsb: Lung diffusing capacity determined by the single-breath technique

$DLCO/V_A$: Carbon monoxide transfer coefficient

BMI: Body mass index

SD: Standard deviation

RR: Relative risk

Introduction

COPD is a high mortality disease, with approximately 2.75 million deaths per year, or 4.8% of all deaths [1]. It is projected to become the third most common cause of death worldwide by the year 2030 [2]. In fact, since 2011, COPD is already the third major cause of death in developed countries such as United States of America [3].

COPD patients usually refer respiratory symptoms, such as dyspnea, chronic cough or sputum production [4, 5], but also present with systemic manifestations of disease, including exercise limitation [6], peripheral muscle impairment [6,7], secondary pulmonary hypertension [8], anemia [9], malnutrition [10] and acute exacerbations leading to hospital admissions [11] and mortality [12].

Pulmonary rehabilitation (PR) is, after smoking cessation, undoubtedly one of the most important multidisciplinary global intervention therapies, not only in the management of respiratory symptoms [13], decreasing dyspnea [14], but also in improving health status [13, 15] and exercise capacity [16], ameliorating psychosocial dysfunction [13], reducing healthcare resource utilization [17, 18], namely reducing hospital readmissions and mortality among patients who received PR after an exacerbation of COPD [19, 20].

It is recognized that patients with COPD who have low levels of daily physical activity have higher mortality rates compared with patients who are more physically active [21]. Therefore, PRP assume a fundamental role in the prognosis of these patients. The long-term survival of patients with chronic respiratory disease who are referred for PR, however, is generally poor, not only because of severely advanced respiratory disease and the negative impact of exacerbations, but also due to the burden of comorbidities [6, 16].

Based on these associations, we have designed a study to determine predictors of 3 years' mortality in advanced stage COPD subjects who have completed a PRP in a respiratory failure day hospital setting. We also investigated factors associated with early (1 year) and late mortality (second and third year), and with less hospital admissions after the program.

Methods

We performed a historical cohort study of baseline characteristics in subjects that completed a PRP in our respiratory failure day hospital, from January 2008 to December 2010.

Inclusion criteria were: diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [4] of FEV_1/FVC ratio after bronchodilator < 0.70, and completion of a PRP program.

PRP had a 12-16 weeks' length and included aerobic exercise training in a treadmill or a cycle ergometer with a target intensity of at least 60% of the initial incremental exercise test, large body muscle strength training, breathing exercises (including breathing control and airway clearance techniques), psychosocial and nutritional support when required, and an individualized or group self-management educational program. These sessions included education on correct use of respiratory medication and the importance of regular physical activity and smoking cessation, as well as identification of symptoms and signs of exacerbation. Subjects were also encouraged to apply a home-exercise routine (stationary cycle at home or regular walking, 30-minutes a day, most days of the week), as a way to enhance activity levels and improve activity of daily living efficacy during and beyond PRP.

Regular medical and physiotherapist follow-up was set, to monitor clinical status and the maintenance of physically active habits.

Population was characterized by sociodemographic factors: gender, age, working status (active or retired), socioeconomic status (economic insufficiency) and cohabitants (living alone, with cohabitants or institutionalized patients). Population was also characterized according to body mass index, smoking habits, lung function tests (FVC, FEV_1, FEV_1/FVC ratio, total lung capacity (TLC), residual volume (RV), lung diffusing capacity determined by the single-breath technique (DLCOsb), carbon monoxide transfer coefficient ($DLCO/V_A$), respiratory failure, comorbidities, bacterial colonization, modified Medical Research Council dyspnea index, functional exercise capacity (6-minute walking distance) [22], use of non-invasive ventilation, long-term

oxygen therapy, hospital admissions due to COPD exacerbations three years prior and after the PRP, history of mechanical ventilation and mortality. All subjects' clinical data were collected from the medical records.

An exploratory analysis was carried out for all variables. Categorical data were presented as frequencies (percentages), and continuous variables as mean and standard deviation (SD) or median and inter-quartile range (25^{th} percentile - 75^{th} percentile), as appropriate.

We analyzed factors associated with early (1 year) and late (second and third year) all-cause mortality. As a secondary end-point, we also looked for factors associated with less hospital admissions for COPD exacerbation in the three years after completing the PRP.

Inter- and intra-group comparisons were completed using paired T-test for continuous variables and Pearson Chi-Square and ANOVA tests for categorical variables. Explanatory variables were assessed using binomial logistic regression. A *P*-value < .05 was deemed significant. All data were analyzed using SPSS Statistics software (IBM, version 20.0, Armonk, New York, United States of America).

Regarding sample size, several factors were considered: Data regarding mortality in COPD is scarce and highly dependent on patients' characteristics (age, smoking habits), disease severity (FEV_1, DLCO, dyspnea, the presence and number of exacerbations, comorbidities, PCO_2) and follow-up time; In the general COPD patients, each of these factors have their own relative risk/hazard ratio, as described, for example, by Nishimura *et al* [23]; Mortality data regarding severe COPD patients undergoing pulmonary rehabilitation programs is inexistent.

Given these conditions, this study ideal (or minimum) sample size is dependent on the tested variable and impossible to present as a single value. As an example, a number based on an extrapolation from data of mortality/survival and hazard ratio defined for each of the above variables in a general COPD cohort is different in several studies [23, 24]. Assuming a type 1 error of .05 (α), a power of 80% and an expected 40% mortality rate in our cohort at 3 years, the number of patients (N) to be enrolled should be between 354 (for a variable with a relative risk of 1.4) and 48 (for a variable with a relative risk of 2.6), as computed for dichotomous variables in PS® software, version 3.0, 2009).

The hospital's ethics committee and administration board approved the trial conduction (IRB: DIRCLIN-22DEZ2014-0430).

Results

Throughout this period, 183 subjects were referred to our unit and completed at least 20 sessions of a PRP. Of this group, 93 patients had COPD and were included in our study: 37 subjects in 2008, 29 subjects in 2009 and 27 subjects in 2010.

Sociodemographic, clinical and functional characteristics of the subjects are reported in Tables 1 and 2. The vast majority of our subjects were male (n=78; 83.9%), with a mean age of 68.6 years (SD=8.9) [Range:43-85 years] and a mean Body Mass Index (BMI) of 25.7 $kg.m^{-2}$ (SD=5.8) [R:14.0-49.3]. Most of our subjects were smokers or former smokers (97.9%) with a mean of 59.9 (SD=30.0) pack-years. When considering economic status, 21 (22.6%) subjects presented with economic insufficiency. Regarding bacterial colonization, 19 subjects (20.4%) were colonized with multi-drug resistant bacteria.

Table 1. Sociodemographic and clinical characteristics of patients with COPD that completed a PRP. Gender, smoking habits (except pack-years), economic insufficiency, working status, cohabitants, comorbidities, respiratory failure, long-term oxygen therapy and NIV are presented in number (%); previous hospital admissions is presented in median (P25-P75) and other data in mean (SD).

SOCIODEMOGRAPHIC CHARACTERISTICS	**All patients**	**Alive patients**	**Deceased patients**	***P*-value**
Gender Male/Female (n=93)	78/15 (83.9/16.1)	48/11 (52.2/12.0)	30/4 (32.2/4.4)	.39
Age (yr) (n=93)	68.6 (8.9)	67 (10)	71 (6)	.10
BMI ($Kg.m^{-2}$) (n=91)	25.7 (5.8)	25.8 (5.4)	25.6 (6.4)	.90
Smoking Habits (n=93)				
- Smokers	11 (11.8)			
- Former smokers	80 (86.0)			
- Never smokers	2 (2.2)			

- Pack-years	59.9 (30.0)	55 (27)	67 (SD=33)	.053
Economic insufficiency (n=93)	21 (22.6)	12 (13.1)	9 (9.8)	.15
Working status (n=88)				
- Active	3 (3.4)	2 (2.3)	1 (1.1)	
- Retired	85 (96.6)	34 (38.6)	51 (58.0)	
Cohabitants(n=92)				
- Alone	7 (7.6)	1 (1,1)	6 (6.5)	
- Cohabitants	81 (88.0)	33 (35.9)	48 (52.1)	
- Institutionalized	4 (4.4)	3 (3.3)	1 (1.1)	
CLINICAL CHARACTERISTICS				
Comorbidities (n=93)				
- Arterial hypertension	50 (53.8)	34 (37.0)	16 (17.4)	.33
- *Heart failure*	41 (44.1)	27 (29.4)	13 (14.1)	.67
- *Cor pulmonale*	19 (20.4)	13 (14.1)	6 (6.5)	.61
- Atrial fibrillation	18 (19.4)	12 (13.0)	6 (6.5)	.075
- *Diabetes mellitus*	15 (16.1)	9 (9.8)	6 (6.5)	.76
- OSA	17 (18.3)	10 (10.9)	7 (7.6)	.66
- TB *sequelae*	25 (26.9)	17 (18.5)	8 (8.7)	.66
- Bronchiectasis	45 (48.4)	29 (31.5)	16 (17.4)	.85
- Interstitial lung disease	7 (7.5)	5 (5.4)	2 (2.2)	.65
- Neoplasm	6 (6.5)	0 (0.0)	6 (6.5)	.001
- Bacterial colonization	20 (21.8)	10 (10.9)	10 (10.9)	.10
- Respiratory failure (n=93)				
- Hypoxemic	31 (33.3)	25 (27.2)	6 (6.5)	
- Hypercapnic	53 (57.0)	27 (29.4)	26 (28.3)	
Long-term oxygen therapy (n=93)	72 (77.4)	45 (48.9)	27 (29.4)	.73
NIV (n=93)	28 (30.1)	11 (12.0)	17 (18.5)	.002
Previous hospital admissions (n=93)	1 (0-3)	1 (0-2)	3 (1-5)	<.001

n: number; yr: years; BMI: Body mass index; OSA: Obstructive Sleep Apnea; TB: Tuberculosis.

Table 2. Functional characteristics associated with 3 years' mortality in patients with COPD after a PRP. S_pO_2 (6MWT) < 90% is presented in number (%), mMRC is presented in median (P25-P75) and other data in mean (SD).

FUNCTIONAL CHARACTERISTICS	All patients	Alive patients	Deceased patients	*P*-value
FEV_1 (L) (n=89)	0.9 (0.3)	1.0 (0.3)	0.9 (0.3)	.16
FEV_1 (%) (n=93)	37.1 (13.7)	38 (14)	35 (14)	.19
FVC (L) (n=90)	2.2 (0.7)	2.3 (0.7)	2.0 (0.7)	.16
FVC (%) (n=92)	69.7 (21.9)	71 (21)	67 (23)	.49
TLC (L) (n=60)	6.6 (1.6)	6.6 (1.6)	6.4 (1.5)	.73
TLC (%) (n=64)	111.3 (21.0)	110 (23)	114 (16)	.43
RV (L) (n=62)	4.3 (1.3)	4.3 (1.4)	4.2 (0.8)	.95
RV (%) (n=68)	180.5 (51.9)	178 (60)	184 (27)	.56
DLCOsb (%) (n=57)	45.6 (21.4)	46 (21)	46 (24)	>.99
D/V_A (%) (n=54)	51.7 (22.7)	51 (22)	55 (27)	.55
mMRC	3.0 (2-4)			
6MWD (m) (n=89)	227.7 (91.5)	243 (91)	198 (87)	.03
S_pO_2 (6MWT) < 90% (n=81)	61 (65.6)	39 (42.4)	21 (22.8)	.25

n: number; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; TLC: Total lung capacity; RV: Residual volume; DLCOsb: Lung diffusing capacity determined by the single-breath technique; K_{CO}: Carbon monoxide transfer coefficient; 6MWD: 6-minute walking distance; 6MWT S_p0_2< 90%: 6-minute walking test with oxygen saturation lower than 90%.

The mean FEV_1 was 37.1% (SD=13.7) [R:9-78]) mean DLCO/sb was 45.6% (SD=21.4) [R:18-108]. Mean functional capacity (6MWD) was 227.7 m (SD=91.5) [R:30-430].

When considering comorbidities, the mean number was 4.98 (SD=2.19) [R:0-10] per patient. The most frequent comorbidities were cardiovascular: 50 (53.8%) subjects had arterial hypertension and 41 (44.1%) subjects had congestive heart failure. The third most frequent comorbidity was bronchiectasis in 45 (48.4%) subjects (Figure 1).

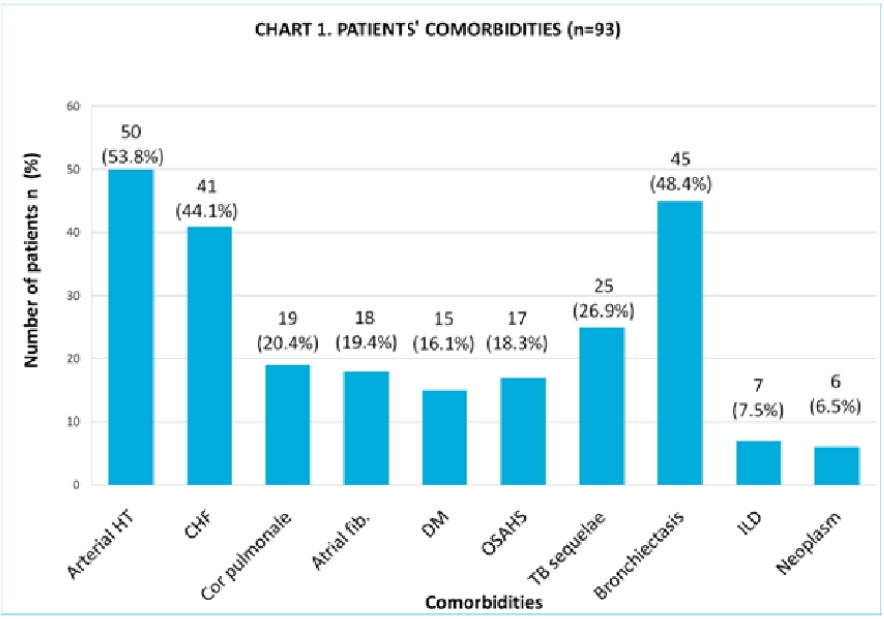

Figure 1. Patients' comorbidities

Arterial HT: Arterial Hypertension; CHF: Congestive Heart Failure; Atril fib.: Atrial fibrilation; DM: *Diabetes mellitus*; OSAHS: Obstructive Sleep Apnea-Hypopnea Syndrome; TB sequelae; Tuberculosis sequelae; ILD: Interstitial Lung Disease.

During the first year after the PRP, 16 subjects died, corresponding to an early mortality of 17.2%. During the second year, 6 subjects died (6.45%) and 12 subjects (12.90%) died during the third year, corresponding to a global (3 years) mortality of 34 (36.6%) subjects.

Throughout the 3 years' period and analyzing the subjects' baseline characteristics, hypercapnic respiratory failure ($P = .02$), non-invasive ventilation ($P = .002$), lung cancer ($P = .001$), shorter 6MWD ($P = .03$) and higher number of previous hospital admissions ($P < .001$) were all associated with a 3 year' higher mortality rate (Tables 1 and 2).

When comparing early *versus* late mortality, the only factor associated with early mortality was atrial fibrillation, although the association was not statistically significant ($P = .050$).

The number of comorbidities was not statistically different between subjects who died *versus* those that were alive 3 years after the PRP [5.06 (SD=2.09) *versus* 4.93 (SD=2.26), P =.79].

In the 3 years' period after PRP, there were less hospital admissions than in the 3 years before, although the difference was not statistically significant [1.7 (SD=2.2) *versus* 2.1 (SD=2.6), P = .17].

When performing logistic regression analysis, previous hospital admissions was the only variable associated with an increased death risk [(Relative Risk (RR) 1.57 (R:1.2-2.0); P = .001; CI:0.95)].

Discussion

In our study there was a high mortality (36.6%) in subjects with COPD in the 3 years after completing a PRP, which might be justified by the severity of airflow limitation (mean FEV_1 of 37.1%), with significant dyspnea in daily-life activities (median mMRC 3) and by a high rate of respiratory failure (n=84; 90.3%). Although the number of comorbidities was not associated with mortality, some comorbidities might have contributed to mortality, such as lung cancer and cardiovascular diseases. Gender and age, as well as smoking habits, were not associated with increased mortality, similar to other studies [25, 26].

This study also evidenced that throughout the 3 years' period, hypercapnic respiratory failure (P = .02), non-invasive ventilation (P = .002), lung cancer (P = .001), shorter 6MWD (P = .03) and higher number of admissions (P < .001) were associated with a higher mortality rate. The presence of respiratory failure and use of non-invasive ventilation also reflected the severity of the disease.

As demonstrated in previous studies, functional exercise capacity, in particular distance in the 6MWT (6MWD), is a strong predictor of mortality in patients with COPD [16, 27]. In fact, 6MWD is a stronger mortality predictor than FEV_1 [28], in part because it is also influenced by other factors: cardiovascular performance, peripheral muscle function, body composition and other comorbidities. The ECLIPSE study [29] enrolling a large

number of subjects with COPD (n=2164) evidenced the prognostic value of 6MWD in mortality. Spruit et al [13] found that a 6MWD threshold of 334 meters predicted an increased risk of death. In our population, mean 6MWD is inferior to this cut-off (227.7 meters). Bowen et al [30] have demonstrated that variables strongly associated with increased survival following a PRP included a higher post rehabilitation functional activities score and higher post rehabilitation 6MWD. Also general daily physical activity, as for instance, standard walking, has proven to be beneficial for these patients, reducing hospital admissions and global mortality [31].

PR in all stages of COPD is an effective and important therapy to improve exercise tolerance, muscle strength, quality of life and decrease respiratory symptoms. Therefore, it should be provided to all symptomatic patients with COPD. It is also fundamental to refer patients with COPD as early as possible (avoiding referral only when patients reach advanced stage disease) in order to improve functional capacity and to further stimulate regular physical activity.

A logistic regression model analysis confirmed that previous hospital admissions was associated with an increased death risk (RR 1.57; P = .001) in the 3 years after the program.

Acute exacerbations of COPD are associated with a lower quality of life and are a risk factor for increased mortality [11, 32] and therefore reducing the number of hospitalizations is a priority in the management of these patients [13]. In our study there were fewer admissions in the 3 year period following PRP, yet it did not reach a statistical significance [1.7 (SD=2.2) *versus* 2.1 (SD=2.6), P = .17], similar to what happened in other studies [17, 18]. This could be explained by the fact that subjects included in our study had severe airflow obstruction and therefore had, in general, more hospital admissions.

In deceased subjects, the only factor associated with early mortality was atrial fibrillation, although this association was not statistically significant (P = .050).

COPD has been associated with an increased prevalence of lung cancer, osteoporosis, anemia, coronary heart disease, anxiety and depression [6]. In fact, COPD is associated with a high prevalence of comorbidities. In a recent study by Areias et al [33], 97% subjects with COPD GOLD IV stage presented, at least, one comorbidity, with an

average of 4 comorbidities per patient. In another study of our group [34], 114 subjects with COPD that were included in PRP had the same high percentage of comorbidities (96.5%). Divo et al [8] have followed 1664 subjects for 51 months recording their comorbidities. They developed a graphic representation system of the prevalence and strength of association with mortality in the form of a "comorbidome". These authors found an average number of comorbidities of 6, and 58.9% of subjects had, at least, one cardiovascular comorbidity. In this study, atrial fibrillation/flutter had a strong association with increased risk for death [HR 1.56, $P = .001$].

Cardiovascular disease, therefore, plays a fundamental role in mortality of patients with COPD [8,33], and our study reflected the higher prevalence of such comorbidities, namely arterial hypertension and congestive heart failure.

Identification and control of risk factors such as smoking, is a key factor for COPD, lung cancer and cardiovascular comorbidities management and might have impact on long-term outcomes, including survival. As demonstrated by Bowen et al [30], the two functional status indicators, the 6MWD and the functional activities sub score, were the strongest predictors of post rehabilitation survival, therefore, PR and an increase in patients' daily physical activity should be encouraged.

This study' limitations include the retrospective nature of the historical cohort, not allowing controlling all variables in the sample of subjects and the possible presence of unidentified confounders.

Secondly, the study population is restricted to subjects attending a PRP in a respiratory failure day hospital unit. Therefore, the findings could only be applicable to that group of severe subjects and we cannot generalize our results to all patients with COPD. Also, the referral of subjects to a PRP could result in a referred bias towards subjects with a greater degree of limitations or symptoms.

Thirdly, there was a high prevalence of male gender and so we cannot extend conclusions to the female gender.

Conclusion

There is a high mortality rate in late stage patients with COPD who underwent a PR program, the most relevant factors associated with mortality being lung cancer, respiratory failure and non-invasive ventilation, severe exacerbations with hospitalization and lower functional exercise capacity. PRP plays a fundamental role by increasing patients' daily physical activity, reducing hospital admissions and global mortality. Also the management of these patients' multiple comorbidities might have impact on long-term outcomes, including survival.

Quick Look

Current Knowledge

COPD is a high mortality disease, projected to become the third most common cause of death worldwide by the year 2030.

COPD clinical manifestations include not only respiratory symptoms but also systemic manifestations, such as exercise limitation, peripheral muscle impairment, secondary pulmonary hypertension, anemia, malnutrition and exacerbations leading to hospital admissions.

Pulmonary rehabilitation (PR) is undoubtedly one of the most important multidisciplinary global intervention therapies.

In recent years, it has been recognized that patients with COPD and low levels of daily physical activity have higher mortality rates compared with patients who are more physically active, but clinical studies have not fully identified mortality predictive factors in severe patients with COPD after a PR program.

What this paper contributes to our knowledge

There is a high mortality rate in late stage patients with COPD. The most relevant factors associated with mortality found in our study were: lung cancer, respiratory failure and non-invasive ventilation, atrial fibrillation, severe exacerbations with hospitalization and lower functional exercise capacity. Severe exacerbations predicted mortality.

In our daily practice, it is important to diagnose and treat as early as possible the comorbidities that patients might present, since controlling such risk factors could improve patients' outcome and survival. Reducing hospitalizations and improving daily physical activities should also be main goals in the management and treatment of patients with COPD, and so, by enabling this, PR becomes a fundamental multidisciplinary intervention therapy that should be promptly offered to these patients.

References

1. WHO. World Health Statistics 2008. Part 1. Ten highlights in health statistics. Available from http:/www.who.int/gho/publications.
2. Raherison C, Girodet PO. Epidemiology of COPD. Eur Respir Rev 2009;18(114):213-221.
3. Hoyert DL, Xu J. Deaths: preliminary data for 2011. Natl Vital Stat Rep 2012;61(6):1-51.
4. GOLD. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2015. Available from: http://www.goldcopd.org.
5. Lindberg A, Sawalha S, Hedman L, Larsson LG, Lundback B, Ronmark E. Subjects with COPD and productive cough have an increased risk for exacerbations and death. Respir Med 2015;109(1):88-95.
6. Cavailles A, Brinchault-Rabin G, Dixmier A, Goupil F, Gut-Gobert C, Marchand-Adam S, et al. Comorbidities of COPD. Eur Respir Rev 2013;22(130):454-475.
7. Mador MJ, Deniz O, Aggarwal A, Kufel TJ. Quadriceps fatigability after single muscle exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;168(1):102-108.
8. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;186(2):155-161.
9. Similowski T, Agusti A, MacNee W, Schonhofer B. The potential impact of anaemia of chronic disease in COPD. Eur Respir J 2006;27(2):390-396.
10. Cote CG. Surrogates of mortality in chronic obstructive pulmonary disease. Am J Med 2006;119(10 Suppl 1):54-62.
11. Marchetti N, Criner GJ, Albert RK. Preventing acute exacerbations and hospital admissions in COPD. Chest 2013;143(5):1444-1454.
12. Quintana JM, Esteban C, Unzurrunzaga A, Garcia-Gutierrez S, Gonzalez N, Barrio I, et al. Predictive score for mortality in patients with COPD exacerbations attending hospital emergency departments. BMC Med 2014;12:66.
13. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013;188(8):e13-64.
14. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2015;2:CD003793.
15. Esteban C, Quintana JM, Aburto M, Moraza J, Egurrola M, Perez-Izquierdo J, et al. Impact of changes in physical activity on health-related quality of life among patients with COPD. Eur Respir J 2010;36(2):292-300.
16. Dajczman E, Wardini R, Kasymjanova G, Prefontaine D, Baltzan MA, Wolkove N. Six minute walk distance is a predictor of survival in patients with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation. Can Respir J 2015;22(4):225-229.
17. Bourbeau J, Julien M, Maltais F, Rouleau M, Beaupre A, Begin R, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. Arch Intern Med 2003;163(5):585-591.
18. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. Thorax 2001;56(10):779-784.

19. Puhan MA, Scharplatz M, Troosters T, Steurer J. Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality -- a systematic review. Respir Res 2005;6:54.
20. Celli B. Pulmonary Rehabilitation in COPD. UpToDate, last update Abr 27, 2015, available from http://www.uptodate.com/contents/pulmonary-rehabilitation-in-copd, Wolters Kluwer Health Clinical Solutions, Phyladephia, PA.
21. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350(10):1005-1012.
22. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166(1):111-117.
23. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002;121(5):1434-1440.
24. Martinez FJ, Foster G, Curtis JL, Criner G, Weinmann G, Fishman A, et al. Predictors of mortality in patients with emphysema and severe airflow obstruction. Am J Respir Crit Care Med 2006;173(12):1326-1334.
25. Hjalmarsen A, Brenn T, Jongsma Risberg M, Meisler Antonsen K, Kristiansen Benum E, Aaseboe U. Retrospective survival in elderly COPD patients receiving pulmonary rehabilitation; a study including maintenance rehabilitation. BMC Res Notes 2014;7:210.
26. Burney P, Jithoo A, Kato B, Janson C, Mannino D, Nizankowska-Mogilnicka E, et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty--a BOLD analysis. Thorax 2014;69(5):465-473.
27. Waschki B, Kirsten A, Holz O, Muller KC, Meyer T, Watz H, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. Chest 2011;140(2):331-342.
28. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax 2006;61(9):772-778.
29. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). Eur Respir J 2008;31(4):869-873.
30. Bowen JB, Votto JJ, Thrall RS, Haggerty MC, Stockdale-Woolley R, Bandyopadhyay T, et al. Functional status and survival following pulmonary rehabilitation. Chest 2000;118(3):697-703.
31. Wouters EF, Franssen FM, Spruit MA. Survival and physical activity in COPD: a giant leap forward! Chest 2011;140(2):279-281.
32. Soler-Cataluna JJ, Martinez-Garcia MA, Sanchez LS, Tordera MP, Sanchez PR. Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. Respir Med 2009;103(5):692-699.
33. Areias V, Carreira S, Anciaes M, Pinto P, Barbara C. Co-morbidities in patients with gold stage 4 chronic obstructive pulmonary disease. Rev Port Pneumol 2014;20(1):5-11.
34. Carreiro A, Santos J, Rodrigues F. Impact of comorbidities in pulmonary rehabilitation outcomes in patients with chronic obstructive pulmonary disease. Rev Port Pneumol 2013;19(3):106-113.

COPD: On Evaluating the Risk for Functional Decline

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Abstract Chronic obstructive pulmonary disease (COPD) is an important cause of chronic morbidity and mortality worldwide. It is characterized by chronic pulmonary and extrapulmonary manifestations with great impact on patients' health, functional impairment, decrease in quality of life and need for prolonged assistance as well as the risk of becoming dependent on others. The aim of this study is to identify COPD patients with the risk of becoming dependent on others to perform activities of daily living (ADL), in order to provide them early intervention and assistance. The study is longitudinal, observational, quantitative and correlational. An intentional sample was used, consisting of patients diagnosed with COPD, clinically stable for at least 3 weeks, who were or had been on a pulmonary rehabilitation program at the Pulmonary Rehabilitation Unit of Hospital Pulido Valente. The IMPALA score is obtained through a questionnaire of self-reported performance for 20 Activities of Daily Living (ADL), assessing the dependent/independent status and four possible early signs of risk of dependence: taking longer to do the activities, reporting difficulty in doing them, having to take breaks while doing them or doing them less frequently. This score was compared with sociodemographic factors, pulmonary function testing (FEV_1), the 6-min walking test (6 MWT) and a disease health-related quality of life score (CAT score). Statistical analysis was performed using exploratory data analysis, visualization techniques and correlation analysis using R. With respect to

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disease characteristics and ADL performance (IMPALA score), COPD Grade D patients showed the worst ADL performance at basal time and a substantial variation at 6 months. Grades A, B and C had most ADL performances close to full capacity and showed little variation after 6 months. ADL performance after 6 months was worse in patients with frequent exacerbations and, although there was no significant correlation to age, older patients tended to improve ADL performance after 6 months. We found a weak correlation between the IMPALA score and exercise functional capacity, but a good correlation with basal health-related quality of life (CAT score). In conclusion, IMPALA score seems to be an additional disease marker evaluating the impact on current functional capacity, well suited to show early risk of incapacity in this group of COPD patients.

Keywords COPD · Health-status · Activities of daily living · Functional capacity

1 Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that represents a major public health problem, for which prevalence tends to rise due to increases in exposure to risk factors and longevity [2, 5, 9].

COPD is an important cause of chronic morbidity and mortality worldwide, causing patients to suffer for a long time and dying prematurely from it or its complications, and is currently the fourth leading cause of death in developed countries [7, 15]. It is a complex disease characterized by chronic pulmonary and extrapulmonary manifestations that impose a great impact on the patients' health, leading to progressive functional impairment, a decrease in quality of life and the need for prolonged assistance.

The loss of capacity to perform activities of daily living (ADL) is a worrying factor of this disease, since it causes a substantial burden on the patients' independence, on their caretakers and on health systems [3, 4].

It is now recognized that no single measure can adequately reflect the nature or severity of COPD [10, 11]. Scientific search of a comprehensive knowledge of COPD morbidity and prognosis led to combining variables such as airway obstruction (FEV_1-forced expiratory volume in 1 s), number of exacerbations (<2 or ≥ 2 hospital visits for respiratory reasons, such as respiratory infections, with or without the need of hospital admission), health status (CAT-COPD Assessment Test) and symptoms (mMRC-modified Medical Research Council dyspnea) deriving the recent multidimensional GOLD classification (categories A, B, C and D) [9] or combining variables such as airway obstruction (FEV_1), mMRC-dyspnea, body mass index and exercise (6 min walking distance in meters) deriving the BODE prognosis index [6].

COPD burden on the patients' ADL performance outlines the need for an early identification of patients who are at risk of becoming dependent on others.

2 Aim

The aim of this study is to identify COPD patients who are at risk of becoming dependent to perform their Activities of Daily Living, using a score to evaluate the patients' current ADL performance.

3 Methods

3.1 Study Design

This is a preliminary study, which is still running, and it is longitudinal, observational and correlational. The study is being conducted at the Pulmonary Rehabilitation Unit/Day-care Hospital for Respiratory Failure Patients' of the Hospital Pulido Valente—Lisbon. The evaluations were applied twice, basal and at 6 months follow up. Exacerbations during that period, requiring hospital assistance, were also tracked. Data collection was undertaken by health care professionals—one pulmonologist and one nurse—and two at the time medical students, who received previous training on the application of the various questionnaires and measures.

3.2 The Sample

An intentional sample was used, consisting of patients diagnosed with COPD, clinically stable for at least 3 weeks, who were or had been on a pulmonary rehabilitation program where the study took place and who consented to participate in the study.

3.3 The IMPALA Score and Questionnaire

The study questionnaire was based on self-reported performance for 20 Activities of Daily Living, namely walking, self-care activities [12, 14] and instrumental activities of daily living [13]. The patients report being dependent or independent on others to perform each ADL and 4 possible early signs of risk of dependence are assessed for each ADL: (1) taking longer, (2) reporting difficulty, (3) having to take breaks, or (4) doing it less frequently. The Impact on Life Activities (IMPALA) Score, is obtained by giving the patients 0 points for each ADL they are dependent on others to perform and 1 point for each ADL they report performing independently. For the patients who are able to perform a task independently 0.2 points are subtracted for each of the four signs of risk of dependence that they report in that ADL. By summing the points for each ADL and multiplying the result by 5 we obtain a score that varies from a

minimum of 0 to a maximum of 100. The difference of the 6 month interval values was called IMPALA Score 6-month variation, with a possible positive variation (a raise ≥1 point), a negative variation (decrease ≥1 point) and a neutral variation (<1 point).

This ADL score, and its 6-month variation, were then compared with sociodemographic factors and measures obtained through standardized instruments, namely, pulmonary function testing (FEV_1), the 6-min walking test (6 MWT) and a health-related quality of life score (CAT Score).

Ethical procedures were followed, informed consent was obtained from all the participants and the trial conduction was approved by the Ethics Committee of the NOVA Medical School (01/2014/CEFCM) and by the Ethics Committee and the administration board of the Centro Hospitalar Lisboa Norte (DIRCLIN-22/05/2014-151).

Data analysis was performed using software R®, making use of descriptive statistics and visualization techniques, exploratory data analysis and non-parametric tests.

4 Results

4.1 Sample Description

The sample's size is 34 patients, all of them caucasian, approximately 15 % female and 85 % male, distributed by age as represented in Table 1.

The *Age* average was 68.4 ± 8.8 years old. Regarding *Education* level, 18 % of the sample reported they could neither read nor write and almost half of the sample (44 %) had a Basic Education level.

Table 1 Sample distribution by age and sex

Variables	Age					
	[45–54]	[55–64]	[65–74]	[75–84]	[85–94]	Total
Sex						
Male	2	6	11	9	1	**29**
Female	0	2	1	2	0	**5**
Total	**2**	**8**	**12**	**11**	**1**	**34**

Table 2 Common comorbidities in the sample

System	%	**Endocrine and metabolic disorders**	
Respiratory system		Type 2 Diabetes mellitus	15
Chronic Respiratory Failure	71	Dyslipidemia	9
Bronchiectasis	27	**Prostatic disease**	21
TB sequelae	18	**Psychiatric disorders**	
Obstructive sleep apnea syndrome	15	Alchoolism	12
Pulmonary thromboembolism	6	Depression	9
Cardiovascular system		**Nutrition disorders**	
Hypertension	62	Excess weight	29
Chronic heart failure	21	Obesity	15
Chronic atrial fibrillation	12	Malnourishment	12
Chronic cor pulmonale	12	Low weight	9
Pulmonary hypertension	12	**Ophtalmology disorders**	12
Ischemic cardiopathy	9	**Osteoarticular disorders**	18
		Gastrointestinal disorders	21

Concerning *F*amily, 58.8 % (n = 20) of the patients were married or in civil union, 18 % were divorced, 15 % were widowed and 9 % were single. About 21 % (n = 7) of the patients reported living alone, 71 % (n = 5) of which were 65 years or above.

As far as *S*moking Habits, we verified that almost all of patients—97 % (n = 33)—were current or former smokers, with an average smoking burden of 66.7 ± 38.9 pack-years and with 65 % (n = 22) of them having smoked 50 pack-years or above.

In terms of *C*omorbidities, we found Chronic Respiratory Failure to be the most common (71 %, n = 24), closely followed by Systemic Hypertension (62 %, n = 21). Most common comorbidities are shown in Table 2.

Of the total sample, only 25 patients completed the 6-month re-evaluation, since 5 of them died in this period (4 of which directly related to respiratory disease), 3 of them haven't yet completed the 6-month period and one was lost to follow-up.

4.2 Combined COPD Assessment (GOLD)

When we applied the Combined COPD Assessment (GOLD) to our sample, we verified that most patients—62 % (n = 21)—were Grade D of the disease, as can be seen in Fig. 1.

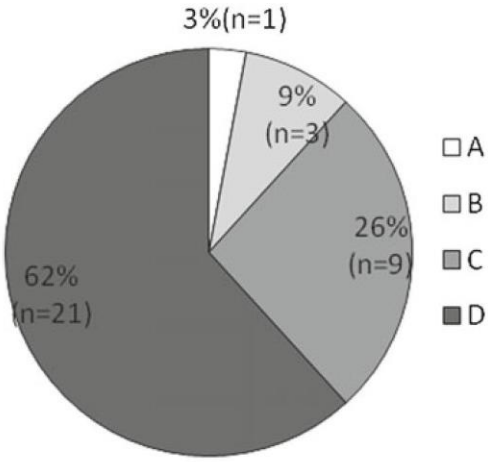

Fig. 1 Sample distribution by COPD grade, according to the Combined COPD Assessment (GOLD)

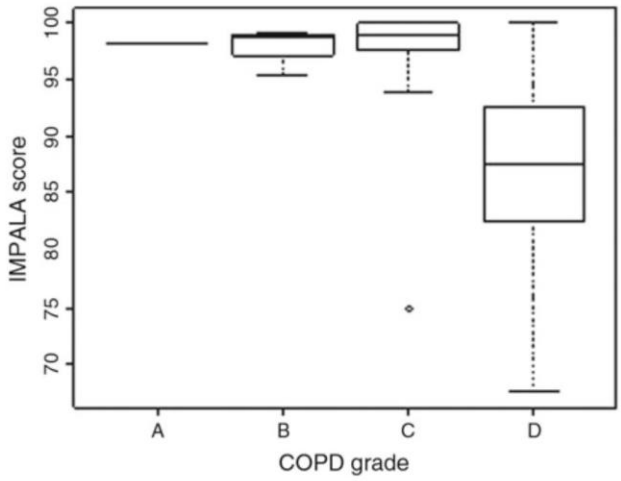

Fig. 2 IMPALA score versus COPD grade

We compared the COPD Grade according to GOLD to IMPALA Score and noticed that Grade D patients had the worst performance, the other categories being near full capacity (Fig. 2). We then compared COPD Grade with IMPALA Score 6 month variation and obtained a scarce variation distribution (Fig. 3).

Within the most severe COPD Grade (D) patients, there was a substantial variation of self-reported functional capacity, either at basal evaluation or after 6 months.

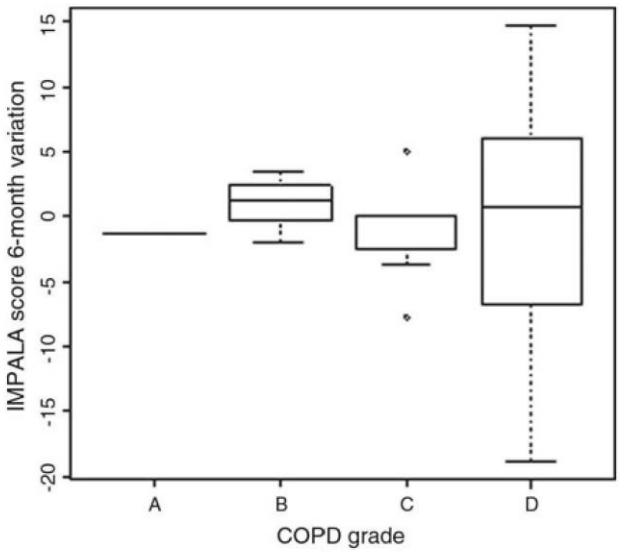

Fig. 3 IMPALA score 6-month variation versus COPD grade

4.3 The IMPALA Score 6-Month Variation

After 6 months, 33 % of the patients improved their ADL performance (IMPALA score), while 37 % had a negative variation. Five (17 %) patients died. 13 % of them had no variation comparing to the first evaluation (Fig. 4).

We tried to identify possible correlations between the IMPALA Score 6-month variation with the variables age, sex, family status, smoking habits and COPD Grade, but found no significant correlation.

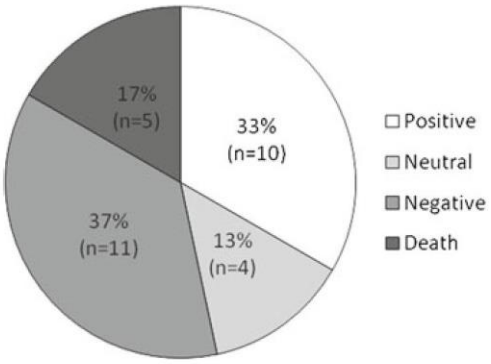

Fig. 4 IMPALA score 6-month variation

4.4 IMPALA Score 6-Month Variation Versus Exacerbations

55 % of the patients with <2 exacerbations in the previous year showed either a positive or neutral variation of the ADL performance (IMPALA score) after 6 months (Fig. 5), 36 % had a negative variation and 9 % died. However, frequent exacerbators (≥2 exacerbations in previous year) showed worse outcomes, with only 22 % experiencing positive or neutral 6-month variation, 33 % having a negative variation and 45 % (n = 4) resulting in death (Fig. 6).

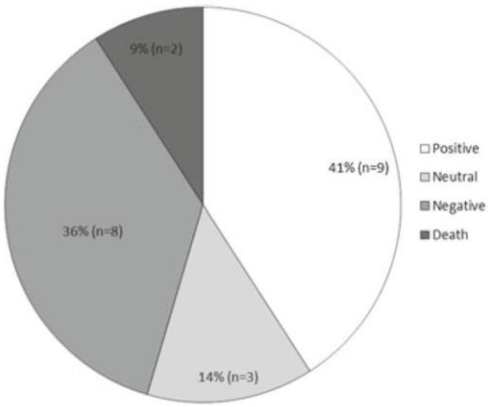

Fig. 5 The IMPALA score 6-month variation in patients with <2 exacerbations

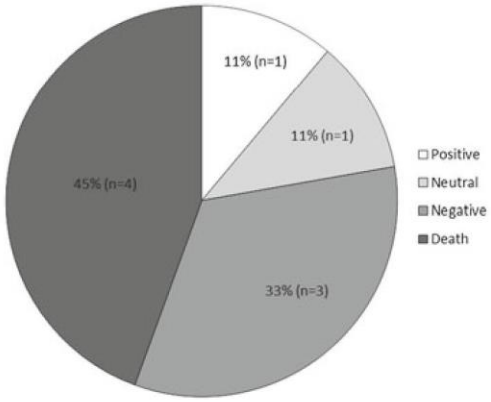

Fig. 6 The IMPALA score 6-month variation in patients with ≥2 exacerbations

4.5 IMPALA Score Versus Age

There was a wide distribution of the IMPALA score at basal time, irrespective of patients age, resulting in a correlation coefficient of −0.15 (Fig. 7). The IMPALA Score 6-month variation according to age (Fig. 8) showed older patients had more positive variations than younger patients, with a correlation coefficient of 0.40, as shown at Fig. 8.

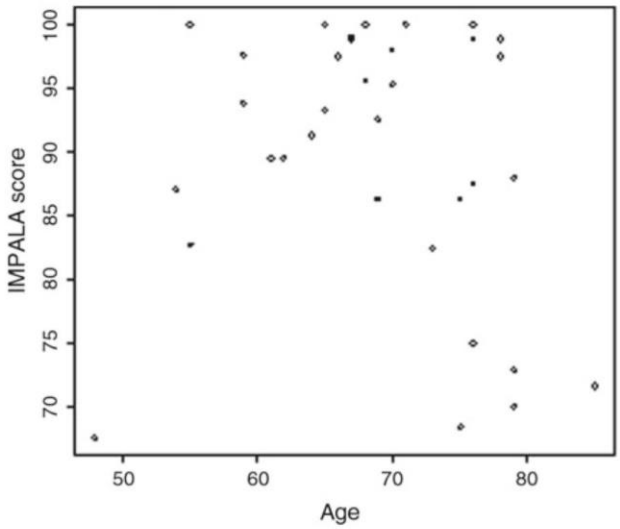

Fig. 7 The IMPALA score according to age, at basal time

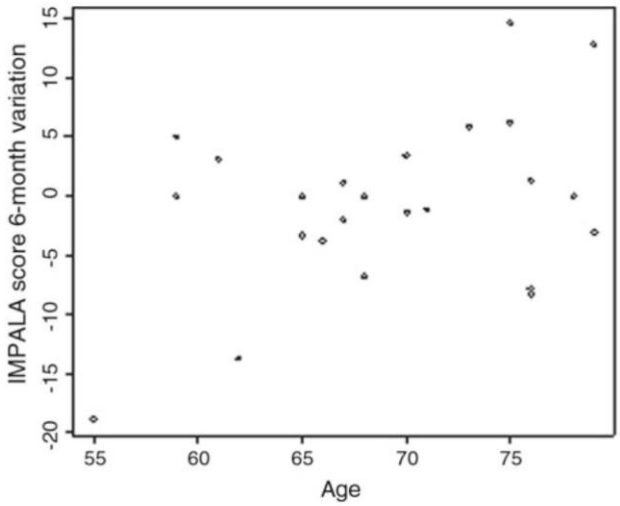

Fig. 8 The IMPALA score according to age, at 6 months

4.6 IMPALA Score Versus 6 MWT

We found a weak correlation between ADL performance (IMPALA score) and exercise functional capacity (6 MWT)—correlation coefficient = 0.29 (Fig. 9). Likewise, after 6 months the variations of both parameters were not related (correlation coefficient = −0.25), see Fig. 10.

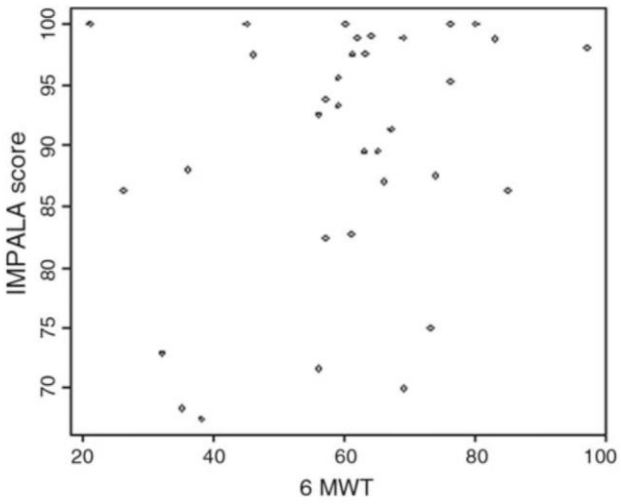

Fig. 9 The IMPALA score according to 6 MWT (m), at basal time

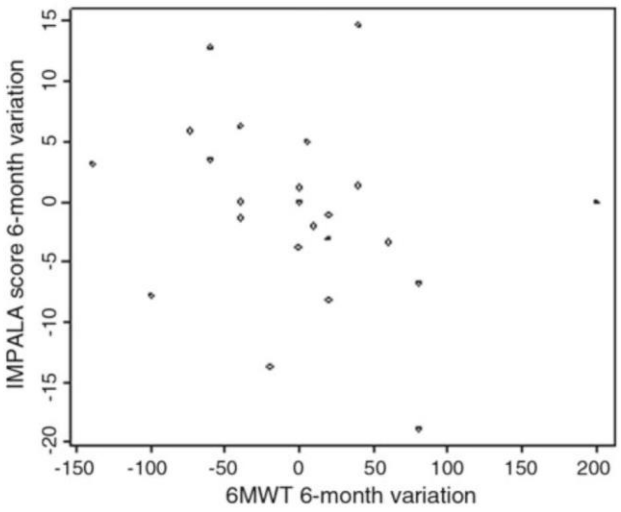

Fig. 10 The IMPALA score 6-month variation according to the 6 MWT 6-month variation

4.7 IMPALA Score Versus CAT Score

We found a good correlation (−0.53) between basal ADL performance (IMPALA score) and health-related quality of life (CAT score), as shown at Fig. 11. After 6 months, variation of both parameters were not related (correlation coefficient = 0.05), see Fig. 12.

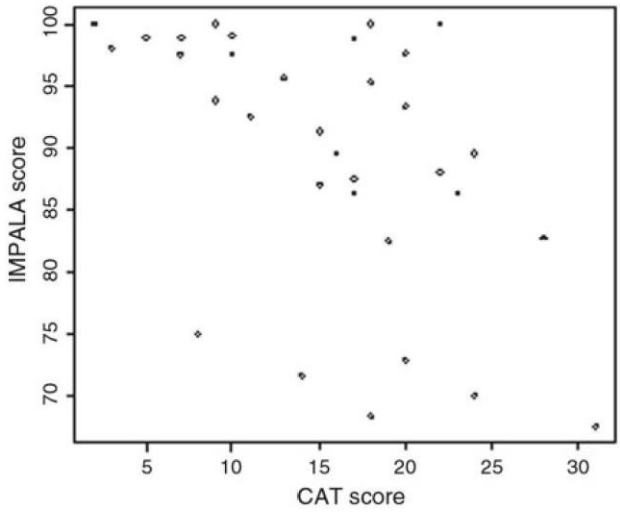

Fig. 11 The IMPALA score according to the CAT score, at basal time

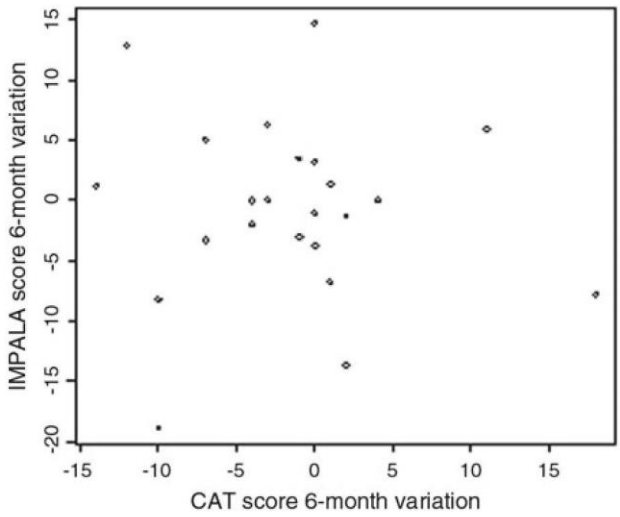

Fig. 12 The IMPALA score according to the CAT score—6-month variation

5 Discussion

The present study, in COPD stable patients engaged in a pulmonary rehabilitation program, was able to identify those at risk of becoming dependent in current daily activities.

With respect to COPD patient's grade, most of them (62 %) were GOLD COPD category D, the most severe one, and showed a significant variation on impact of disease reported activities of daily living. Other authors also evidenced a substantial heterogeneity in COPD patients. In ECLIPSE study [1], the severity of airflow limitation in COPD patients was poorly related to the degree of breathlessness, health status, presence of co-morbidity, exercise capacity and number of exacerbations reported in the year before the study. The distribution of these variables within each GOLD stage was wide. Even in subjects with severe airflow obstruction, a substantial proportion did not report symptoms, exacerbations or exercise limitation. The clinical manifestations of COPD are highly variable and the degree of airflow limitation does not capture the heterogeneity of the disease [1].

From the COPD disease markers, exacerbations are important contributors to accelerate health status decline and increase health related costs [16]. In line with these data, in our study, frequent exacerbator patients ($\geq$2 exacerbations in previous year) showed a predominantly negative variation on the functional capacity after 6 months, while more than half of infrequent exacerbators showed either a positive or neutral variation.

There was a wide variation of ADL performance (IMPALA score) irrespective of patient's age, which reinforces the notion that age is no more than one of the factors contributing to the overall patient's status. Nevertheless, older patients tended to improve ADL performance after 6 months, which is consistent with the recognized benefits of physical activity that counteracts the aging progressive reduction of maximum abilities [8]. As such, ageing COPD patients are suitable candidates for pulmonary rehabilitation, with improvement of domestic function and physical activity [17].

The correlation analysis between the IMPALA Score 6-month variation and other variables like age, sex, family status, smoking habits and COPD Grade might be limited by the reduced number of observations. Additional studies with larger samples could allow further investigation of these correlations.

In this preliminary study, ADL performance (IMPALA score) showed a stronger association with health-related quality of life (CAT score) than with exercise functional capacity (6 MWT). All these variables translate COPD impact on patient's health and wellbeing. Probably they constitute different dimensions of this clinical entity, ADL performance being related to current low demanding tasks, thus complementing the holistic evaluation in each patient.

6 Conclusion

Self-reported ADL performance (IMPALA score), based on 20 ADL tasks performance limitations, seems to be an additional disease marker, eliciting the impact on current functional capacity and having a good correlation with basal health-related quality of life, as measured by CAT score.

In COPD patients, ADL performance (IMPALA score), as a marker of current functional capacity showed: (1) heterogeneity among the most severe GOLD grade D patients; (2) negative impact of frequent exacerbations; (3) age as not specifically related; (4) complementary information gathered by the 6 MWT that evaluates submaximal exercise capacity.

In conclusion, we believe that a simple and easy to implement evaluation of ADL performance (IMPALA score)—is well suited for early detection of risk of incapacity in this group of COPD patients.

References

1. Agusti, A.: COPD heterogeneity in the ECLIPSE cohort. Respir. Res. **11**, 122 (2010)
2. Bárbara, C., Rodrigues, F., Dias, H., Cardoso, J., Almeida, J., Matos, M.J., Simão, P., Santos, M., Ferreira, J.R., Gaspar, M., Gnatiuc, L., Burney, P.: Prevalência da doença pulmonar obstrutiva crónica em Lisboa, Portugal: estudo Burden of Obstructive Lung Disease. Rev. Port. Pneumol. **19**(3), 96–105 (2013)
3. Botelho, A.: Autonomia Funcional em Idosos. Caracterização multidimensional em idosos utentes de um centro de saúde urbano (1ł ed.). Laboratórios Bial, Porto (2000)
4. Botelho, A.: Método de Avaliação Biopsicossocial—um instrumento de detecção em saúde. In: Fernandes, L., Pereira, M.G., Pinto, L.C., Firmino, H., Leuschner, A. (eds.) Jornadas de Gerontopsiquiatria 1ł Edição, pp. 87–89 (2011)
5. Buist, A.S., McBurnie, M.A., Vollmer, W.M., Gillespie, S., Burney, P., Mannino, D.M. et al.: BOLD Collaborative Research Group. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet **370**, 741–750 (2007)
6. Celli, B.R., Cote, C.G., Marin, J.M., Casanova, C., de Montes, O.M., Mendez, R.A., Pinto-Plata, V., Cabral, H.J.: The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N. Engl. J. Med. **350**, 1005–1012 (2004)
7. Chapman, K.R., Mannino, D.M., Soriano, J.B., Vermeire, P.A., Buist, A.S., Thun, M.J. et al.: Epidemiology and costs of chronic obstructive pulmonary disease. Eur. Respir. J. **27**, 188–207 (2006)
8. Darren, E.R., Warburton, D.E., Nicol, C.W., Bredin, S.S.D.: Health benefits of physical activity: the evidence. CMAJ **174**(6) (2006). doi:10.1503/cmaj.051351
9. Global Initiative for Chronic Obstructive Lung Disease—GOLD: global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. Available on the GOLD. www.goldcopd.org (2013)
10. Jones, P.W.: Health status and the spiral of decline. COPD J. Chronic Obstr. Pulm. Dis. **6**, 59–63 (2009)
11. Jones, P., Miravitlles, M., Molen, T., Kulich, K.: Beyond FEV1 in COPD: a review of patient-reported outcomes and their measurement. Int. J. Chronic Obstr. Pulm. Dis. **7**, 697–709 (2012)
12. Katz, S., Ford, A.B., Moskowitz, R.W., Jackson, B.A., Jaffe, M.W.: Studies of illness in the aged: the index of ADL; a standardized measure of biological and psychosocial function. JAMA **185**, 914–919 (1963)

13. Lawton, M.P., Brody, E.M.: Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist **9**, 179–186 (1969)
14. Mahoney, F.I., Barthel, D.W.: Functional evaluation: the Barthel index. Md. State Med. J. **14**, 61–65 (1965)
15. Raherison, C., Girodet, P.O.: Epidemiology of COPD. Eur. Respir. Rev. **18**, 213–221 (2009)
16. Seemungal, T.A., Hurst, J.R., Wedzicha, J.A.: Exacerbation rate, health status and mortality in COPD—a review of potential interventions. Int. J. Chronic Obstr. Pulm. Dis. **4**, 203–223 (2009)
17. Sewell, L., Singh, S.J., Williams, J.E., Collier, R., Morgan, M.: Can individualized rehabilitation improve functional independence in elderly patients with COPD? Chest **128**, 1194–1200 (2005)

Acute exercise amplifies inflammation in obese COPD patients – a prospective cohort exploratory study

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Abstract

Background

Systemic inflammation has been associated with the pathogenesis of chronic obstructive pulmonary disease (COPD) systemic effects. However, persistent systemic inflammation is absent in most of COPD patients, and even after exacerbations and exercise, scientific evidence presents conflicting results. We aim to evaluate inflammatory gene expression at rest and at one and 24 hours after exhausting exercise in COPD patients and search for patients' variables associated with inflammatory expression.

Methods

A prospective cohort study was conducted in COPD patients recruited when entering a pulmonary rehabilitation (PR) program. Demographic, clinical and functional data were collected. Blood samples were collected and gene expression was analysed by reverse transcriptase polymerase chain reaction for IFNg, IL1b, IL6, IL8, TNFa, TGFb1 and iNOS.
The study included 21 patients (15 men, 71.4%), mean age 66.1 years old (SD=8.27), mean FEV_1 46.76% (SD 20.90%), 67% belonging to GOLD grade D, mean BODE index of 3.9, 90.5% with smoking history, mean BMI 25.81 (SD=4.87), median of 1.29 exacerbations in the previous year.

Results

We found an association between BMI and inflammatory expression at all time points, a slight inverse association occurs with low BMI for mRNA IL1b, IL6, TNFa, TGFb1 and iNOS, and a more pronounced positive association for obese patients for all gene tested.
Inflammation in COPD has been associated with worst prognosis.

Conclusion

This preliminary study evidenced obesity as a potential relation between COPD and systemic inflammation. Therapeutic approaches directed to obesity, such as PR with exercise training, self-management education and nutrition counseling might contribute to improve COPD prognosis.

Key-words: *COPD; inflammation; exercise; obesity; Reverse Transcriptase Polymerase Chain Reaction*

Introduction

Chronic obstructive pulmonary disease (COPD) is associated with important extrapulmonary manifestations, including weight loss, skeletal muscle dysfunction, cardiovascular disease, depression, osteoporosis, reduced exercise tolerance, and poor health status (1-3). Although the pathobiology of COPD has not yet been fully determined, persistent systemic inflammation has been associated with the pathogenesis of the majority of these systemic effects (3, 4). Elevated circulating levels of white blood cells, C-reactive protein (CRP), interleukins 6 (IL-6) and 8 (IL-8), fibrinogen and tumor necrosis factor alpha (TNFa) have been reported in patients with COPD (5). However, systemic inflammation is absent in a large group of COPD patients, as shown in several studies (6, 7).

The role of exercise in COPD inflammatory process has also been a source of scientific debate (6, 8-16). Patients with COPD are exposed to a systemic inflammation that is amplified by exhaustive exercise. Inflammatory response to exercise is more pronounced in COPD patients when compared to healthy controls, even at lower levels of exercise intensity (9, 17). However, scientific literature remains not consensual about this subject, as several studies showed a reduction in the level of TNFa protein expression in COPD subjects (10-12). As pointed by Canavan and colleagues (13), some heterogeneity of these results might be caused by the different methods used in the studies (patient characterization, exercise protocols, and assay techniques). Crul and colleagues (14) did not find any evidence of muscle inflammation in COPD patients independently of being in a stable or acute exacerbation state. Contrariwise, an anti-inflammatory effect of regular exercise is suggested in some low systemic inflammation chronic diseases, with positive outcomes in disease prevention and symptomatic improvement (6, 15, 16).

In this study we aim to evaluate the inflammatory and immune regulatory gene expression profiling in peripheral blood determined at rest in COPD patients, and its possible modification after exhausting exercise, searching for variables and patients' characteristics associated with inflammatory expression. Our hypothesis is that exercise might enhance inflammatory expression with clinical consequences.

Material and methods

Patients

A prospective cohort study was conducted on a sample of 21 patients with diagnosed COPD, according to the Global Initiative for Obstructive Lung Disease Project (GOLD) (2) as post bronchodilator $FEV_1/FVC < 0.70$. Patients were consecutively recruited when entering in a pulmonary rehabilitation (PR) program at our PR Unit, from January to December 2010. Participants were selected if clinically stable in the previous four weeks and able to exercise and answer health status questionnaires. Patients diagnosed with other significant lung diseases, eg. asthma, bronchiectasis or other conditions that might cause dyspnea or affect exercise performance, were excluded.

Data Collection

Data collection included age, body mass index (BMI), smoking history, number of exacerbations in the previous year and comorbidities. Clinical data was obtained by interview and accessing medical records, including the review of concomitant medications. Charlson (18), Charlson-age (19) and COTE (COPD specific comorbidity test) (20) indexes were calculated based on comorbidities data. Participants completed questionnaires on dyspnea (modified Research Council breathlessness scale and Mahler' baseline dyspnea index) (21), activities of daily living (London Chest Activity of Daily Living scale - LCADL) (22), anxiety and depression (Hospital Anxiety and Depression scale – HADS) (23), and health status (St. George's Respiratory Questionnaire – SGRQ) (24).

Pulmonary function data were obtained using standardized equipment (SensorMedics Corporation, Yorba Linda, CA, USA) according to ERS/ATS consensus guidelines (25-27). Post-bronchodilator spirometric values were obtained. Data was measured as absolute values (L) and as percent predicted from reference values (28).

Exercise test and laboratory procedures

Patients were subjected to an incremental exercise test to maximum tolerated in a treadmill or cycle ergometer (Figure 1). Treadmill protocol started with a three minutes warming up at 2.0 Km/h and 0º inclination, followed by 0.5 km/h increments per minute and 0º inclination until the patient attained a brisk walking without running, and then increments of 2º inclination each minute until patients' exhaustion. Cycle ergometer protocol started with a three minutes warming up without any resistance, followed by 10 W of increments each minute until patients' exhaustion. Safety criteria for ending the exercise test were applied according to ATS/ACCP guidelines (29).

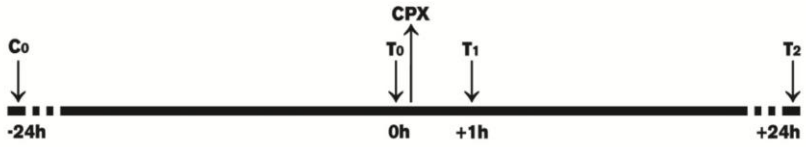

Figure 1 - Blood sampling scheme and exercise test (CPX).

Whole blood samples were collected from each patient at three different time points: at rest (T0), and at one hour (T1) and 24h (T2) after the exercise test. Additionally, a blood sample from the first ten patients enrolling the study was collected the day before (C0), and considered as a calibration sample for relative gene expression analysis to establish the expression pattern of targeted genes in the resting condition. These participants were told to maintain usual low-intensity activities of daily living and avoid exercising above that intensity in the previous 48 hours.

RNA integrity from blood cells was immediately preserved at collection with the PAXgene Blood RNA Tubes (PreAnalytiX GmbH, Hombrechtikon, Switzerland). Each sample tube was kept at room temperature for 2 hours, followed by incubation at -20°C for 24 h and thereafter stored at -80°C. Thawed tubes were processed with the PAXgene Blood RNA Kit (PreAnalytiX GmbH) for isolation of total RNA according to manufacturers' instructions, including DNAse digestion. Yield of purified RNA samples was evaluated with a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Wilmington, USA) and stored at −80°C. Gene expression was analysed by reverse transcriptase polymerase chain reaction (RT-PCR),

essentially as previously described (30). Briefly, a template cDNA was generated by reverse transcription from 1 to 2 μg of total RNA using the High Capacity cDNA Archive Kit (Applied Biosystems, Foster City, CA). Measurements of targeted genes and endogenous control (beta actin) were performed using the Taqman Gene Expressions Assays in combination with TaqMan Fast Advanced Mastermix on a 7900 HT system (Applied Biosystems), according to manufacturers' instructions. The analyzed genes and each primer/probe assay ID were the following: interleukin 1 beta (IL-1β, Hs00174097_m1), interleukin 6 (IL-6, Hs00174131_m1), interleukin 8 (IL-8, Hs00174103_m1), inducible nitric oxide synthase (iNOS, Hs00167248_m1), interferon gamma (IFN-γ, Hs00174143_m1), tumour necrosis factor (TNF-α, Hs00174128_m1), transforming growth factor beta 1 (TGF-β1, Hs00998133_m1). The efficiency for each primer/probe assay was above 95% (as determined by the manufacturer).

Endogenous gene expression was used for each assay normalization and gene expression was calculated by the adapted formula $2^{-DCt}*1000$, which infers the number of mRNA molecules of the gene of interest per 1000 molecules of the endogenous controls (31). DCt stands for the difference between the cycle threshold of the target gene and that of the endogenous control genes.

A week after the maximum exercise test, patients performed a 6-minute walking test (6MWT), standardized according to international guidelines (32). 6MW distance, FEV_1 % predicted after bronchodilator, mMRC dyspnea scale and BMI data were aggregated to calculate BODE index (33).

Subjects were willing and able to participate in this study and gave written informed consent prior to baseline measurements. The hospital's Ethical committee and administration board approved the trial conduction (IRB: Study 25/07_ CE/027/07), and all data was processed anonymously according to the institution's privacy policy.

Statistical analysis

Categorical data were presented as frequencies and percentages, and continuous variables as mean or median, SD or interquartile range: 25th percentile (P_{25}) to 75th percentile (P_{75}). To verify the normality assumption of parametric tests, Shapiro-Wilk goodness-of-fit test and Q-Q plots were used. To compare genetic inflammatory markers between T0 and C0, T0 and T1, and T0 and T2, nonparametric tests were used (exact Wilcoxon signed ranks test or sign test

when the differences had no symmetric distributions). To identify associations between patients' characteristics and genetic inflammatory expression in all time points, LOWESS (Locally Weighted Scatterplot Smoother), Spearman's correlation coefficient and Mann-Whitney test were applied. The significance level α=0.05 was considered. Due to the exploratory nature of the study, no multiple testing procedures were used.

All data was analysed using the Statistical Package for the Social Sciences for Windows 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

Results

A total of 21 patients were recruited, accepted to participate and enrolled the study. There were no dropouts. Participants sample included 15 men (71.4%), with a mean age of 66.1 years (SD=8.27), 19 (90.5%) with smoking history (16 previous smokers - 76.2% and 3 active smokers - 14.3%), with an average 69 pack-years (range 12 to 150) and 2 non-smokers (9.5%). Fourteen patients (66.6%) had respiratory failure, 54.1% hypoxemic and 9.5% hypercapnic.

According to GOLD categories (34), 14 (67%) patients belonged to category D. Mean FEV_1 was 46.76 % (SD=20.90%, min 21%, max 97% predicted), median BODE was 3.9 (min 0 , max 8) and a median of 1.3 exacerbations (min 0, max 10) occurred in the previous year.

Mean BMI were 25.81 $Kg.m^{-2}$ (SD=4.9), ranging from 17 to 34 $Kg.m^{-2}$. Three participants (14%) were malnourished and 12 (57%) were overweight or obese. The most prevalent comorbidities in our sample were cardiovascular disease, being arterial hypertension the most prevalent (52.4%).

Mean 6MWD was 346.1 meters (SD=86.1), ranging from 185 to 520 meters. Oximetry lowest values at 6 minute walking test were on average 85%, ranging from 68% to 94%. Baseline characteristics are presented in Table 1.

Table 1 - Baseline characteristics of COPD participants. Spirometry values displayed are post-bronchodilator.

Demographics	
Gender m/f n (%)	15 (71.4%) / 6 (28.6%)
Age years mean (SD) min-max	66.05 (8.27) 50-82
BMI Kg.m-2 mean (SD) min-max	25.81 (4.87) 17-34
Pack's mean (SD) min-max	69.05 (30.85) 12-150
Symptoms/Health status	
mMRC median (min-max)	1.00 (0-3)
Mahler's BDI median (min-max)	7.00 (3-10)
LCADL median (min-max)	19.15 (8-36)
HADS-anxiety median (min-max)	6.19 (1-14)
HADS-depression median (min-max)	5.62 (0-12)
SGRQ median (min-max)	45.95 (27-77)
BODE median (min-max)	3.90 (0-8)
Exacerbations previous year median (min-max)	1.29 (0-10)
GOLD categories A / B / C / D n (%)	2 (9.5) /2 (9.5) /3 (14.3)/14(66.6)
Comorbidities	
COTE median (min-max)	1.24 (1.87) 0-8
Charlson median (min-max)	1.62 (0.81) 1-3
Charlson-age median (min-max)	3.57 (0.93) 2-5
Respiratory failure/hypoxemic /hypercapnic n (%)	14 (66.6) / 12 (54.1) / 2 (9.5)
Cardiovascular comorbidities n (%)	15 (71.4)
Arterial hypertension n (%)	11 (52.4)
Congestive heart failure/Cor pulmonale n (%)	5 (23.8)
Ischemic heart disease n (%)	2 (9.5)
Arrythmias n (%)	2 (9.5)
Tuberculous sequelae n (%)	7 (33.3)
Bronchiectasis n (%)	2 (9.5)
Obesity or overweight n (%)	12 (57.1)
Malnourished n (%)	3 (14.3)
Diabetes mellitus n (%)	1 (4.8)
Dyslipidemia n (%)	4 (19.0)
Osteoarticular pathology n (%)	4 (19.0)
Physiology	
FVC L mean (SD) min-max	2.75 (0.95) 0.84-5.31
FVC % mean (SD) min-max	85.52 (23.74) 32-139
FEV_1 L median (P25-P75) min-max	1.02 (0.73-1.46) 0.47-3.25
FEV_1 % mean (SD) min-max	46.76 (20.90) 21-97
FEV_1/FVC% mean (SD) min-max	43.48 (14.11) 21-69
TLC L (n=19) mean (SD) min-max	7.11 (1.37) 4.14-8.71
TLC % (n=19) mean (SD) min-max	121.53 (15.64) 86-155
RV L (n=19) mean (SD) min-max	4.26 (1.27) 2.51-6.43
RV % (n=19) mean (SD) min-max	189.79 (49.19) 128-293
DLCO % (n=17) mean (SD) min-max	45.12 (19.07) 16-95
KCO % (n=17) mean (SD) min-max	41.41 (17.49) 13-76
PaO_2 mmHg mean (SD) min-max	65.46 (8.58) 50-77
$PaCO_2$ mmHg median (P25-P75) min-max	42.10 (37.20-46.05) 35-60
6MWD m mean (SD) min-max	346.05 (86.06) 185-520
6MWT SpO_2 % mean (SD) min-max	84.57 (6.67) 68-94

8

Laboratory results

In the first 10 patients studied, we did not find a statistical significant difference between C0 and T0, the two time points of baseline resting condition (Annex-Table 1a). In the entire sample, there was no statistical significant difference between inflammatory expression at rest and at 1 hour and 24 hours after the maximal exercise test (Table 2).

Table 2 - Median (P_{25}-P_{75}) of the mRNA inflammatory genes at rest (T0), and at 1 hour (T1) and 24 hours (T2) after maximal exercise test. Comparison of T1 versus T0 and T2 versus T0.

	T0	T1	T1 *vs* T0 p	T2	T2 *vs* T0 p
IFNg	0.16 (0.04-1.57)	0.19 (0.06-0.95)	1.000*	0.15 (0.05-1.17)	0.739**
IL1b	15.46 (6.42-266.69)	19.38 (7.39-268.48)	0.383*	23.15 (5.63-250.58)	0.664*
IL6	0.33 (0.11-2.81)	0.51 (0.23-2.67)	0.189*	0.59 (0.10-2.05)	0.815*
IL8	1.82 (0.97-69.57)	4.70 (1.87-43.26)	0.189*	2.07 (0.94-43.37)	0.664*
TNFa	2.99 (2.55-47.00)	3.36 (2.25-29.61)	1.000*	3.42 (2.51-38.21)	0.383*
TGFb	199.71 (64.86-5462.36)	224.38 (63.91-4456.02)	0.383*	373.45 (75.18-5250.38)	0.078*
iNOS	0.03 (0.01-0.29)	0.04 (0.01-0.60)	0.791*	0.04 (0.01-0.31)	0.398**

*Sign Test
** Exact Wilcoxon Signed Ranks Test

Screening associations between patients' characteristics and inflammation, the only association found was between BMI and inflammatory expression at all time points. As presented in Figure 2, a slight inverse association occurs with low BMI (values under 20 $Kg.m^{-2}$) for inflammatory genes mRNA IL1b, IL6, TNFa, TGFb and iNOS. Moreover, a more pronounced positive association was found for obese patients (BMI above 30 $Kg.m^{-2}$) for all inflammatory mRNA gene tested, at all time points.

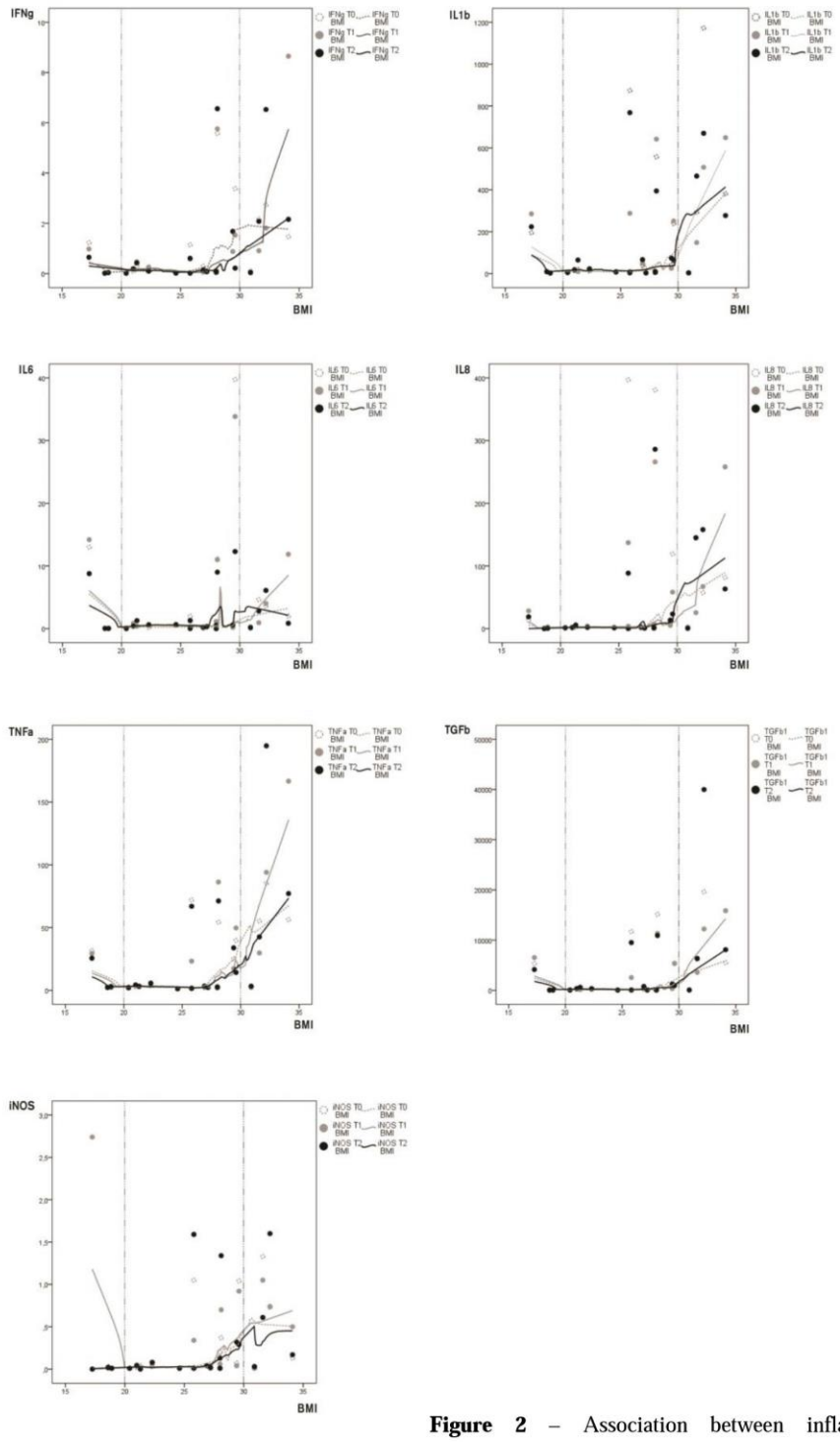

Figure 2 – Association between inflammatory biomarkers at rest (T0) and at 1 hour (T1) and 24 hours (T2) after maximal exercise test and body mass index. A Lowess was fitted to the data. Lowess – Locally weighted scatterplot smoother.

10

We found no associations between inflammatory expression and all other patients' characteristics and variables [examples are shown in Annex-Figure 1a for age, FEV_1 (% predicted) and 6MWD].

Due to the previously reported potential influence of cardiovascular comorbidity in the inflammatory expression of COPD patients (35), we looked for the association between this variable and inflammatory gene expression. Higher values of these expressions were consistently found (sometimes with statistical significance) for patients without cardiovascular comorbidity (Annex-Table 2a).

Discussion

In our COPD patients' sample, real-time polymerase chain reaction of the target mRNA inflammatory genes did not show increased inflammation either at rest or after a maximum exercise test. When looking at the inflammatory expression measured in resting samples on two consecutive days (control group), there were also no statistical differences between the two time-points, which might reflect stability at rest mRNA parameters.

Persistent systemic inflammation is not a universal finding in patients with COPD. ECLIPSE study recently showed that in 1755 COPD patients, about 30% did not have systemic inflammation, and only a minority (16%) had persistent inflammation during 1 year follow up (5).

We did not find a significantly different mRNA inflammatory expression at 1 and at 24 hours after maximal exercise. However, in the subgroups of malnourished and obese COPD patients, we found opposite associations with mRNA inflammatory expression. Malnourished patients showed a tendency to lower mRNA levels of iNOS, IL6, IL1b, TNFa, and TGFb1 when increasing BMI towards normal values. Contrariwise, overweight and obese patients evidenced higher mRNA levels of TNFa, IFNg, IL1b, IL8, TGFb1, iNOS and IL6 as their BMI increased above normal values. ECLIPSE study also evidenced high BMI as one of the independent risk factors for persistent inflammation, both at baseline and at one year follow-up (5). This association was not evident for fat free mass index, which suggests an important role for adipose tissue in systemic inflammation. Garcia-Aymerich and colleagues (36) also identified a "systemic" COPD subtype characterized by a higher proportion of obesity in 342

COPD patients with a significant systemic inflammation; this pattern was maintained through a 4 years' follow-up period. Studies have also confirmed that an acute phase response evidenced by serum levels of C-reactive protein is increased in obesity and associated with insulin resistance (37).

Most of the scientific evidence has previously shown that peripheral muscle atrophy and cachexia are associated with systemic inflammation in patients with COPD, when compared to patients with no muscle wasting (38, 39). Likewise, in our study, malnutrition was also associated with higher expression on mRNA genes iNOS, IL6, IL1b and TGFb1, but with a less extent, and in the opposite way, when compared to what happened in patients with higher BMI.

Inflammation in COPD has been associated with worst prognosis (40). At ECLIPSE study, persistent inflamed patients had significantly increased all-cause mortality and exacerbation frequency compared with non-inflamed patients (5). In our study, 8 patients were dead after 4 years (38%), of whom, 4 (50%) were obese or overweighed, and 3 (37.5%) were malnourished. Only one dead patient had had a normal BMI at baseline (data not shown).

Cardiovascular disease is the most prevalent comorbidity in COPD (41-43), and it is previously associated with systemic inflammation (elevated C-reactive protein) in patients with COPD (35). However, although prevalent (71%), cardiovascular disease was not associated with higher inflammatory expression for all studied genes.

There is still an unmet need to characterize different COPD phenotypes that might benefit from different treatment approaches and respective outcomes. Inhaled corticosteroids, as an example, have limited efficacy in the reduction of systemic inflammation in COPD (44). On the other hand, a non-pharmacological approach, such as pulmonary rehabilitation with exercise training, has proven to improve exercise tolerance, while modifying body composition towards a higher fat-free mass, improving muscle function, and, as evidenced by some studies, it might also attenuate systemic inflammation (6).

The present study has a number of limitations that need to be addressed. A small sample size was not able to rule out the presence of an increased systemic inflammation. Although small, this sample size was enough to graphically show an association between BMI and inflammation. It is an exploratory study and larger longitudinal studies are needed to confirm this association.

Another limitation might be the fact that levels of plasma proteins and related mRNA precursors are sometimes not coincident (45, 46). Cytokine protein production is strictly regulated at multiple steps, including transcription (mRNA chain generation) and translation (protein synthesis from RNA). Plasma cytokine expression will depend on the efficiency of translation of mRNA into useful proteins.

Although our study evidenced an association between obesity and several inflammatory genes, and other authors also evidenced RT-PCR as an attractive method to study the gene expression of cytokines in whole blood (47), an additional study should be carried out to confront mRNA genes and the corresponding plasma proteins.

Future

Exercise training induces a body composition modification, with greater muscle strength and mass and reduction in body fat (48). Large prospective or interventional studies focused on systemic inflammation are needed to acknowledge the role of exercise training or regular physical activity in controlling systemic inflammation in COPD patients.

Conclusion

This preliminary study evidenced an association between BMI (malnutrition and obesity) and the levels of inflammatory mRNA cytokine precursors, evidencing obesity as a potential link between COPD and systemic inflammation.

References

1. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009; **33**(5)**:** 1165-85.

2. Garcia-Rio F, Miravitlles M, Soriano JB, Munoz L, Duran-Tauleria E, Sanchez G *et al.* Systemic inflammation in chronic obstructive pulmonary disease: a population-based study. *Respir Res* 2010; **11**(63)**:** 1-15.

3. Agusti AG. Systemic effects of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; **2**(4)**:** 367-70; discussion 371-2.

4. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004; **59**(7)**:** 574-80.

5. Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE *et al.* Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012; **7**(5)**:** e37483.

6. van der Vlist J, Janssen TW. The potential anti-inflammatory effect of exercise in chronic obstructive pulmonary disease. *Respiration* 2010; **79**(2)**:** 160-74.

7. Van Helvoort HA, Heijdra YF, Thijs HM, Vina J, Wanten GJ, Dekhuijzen PN. Exercise-induced systemic effects in muscle-wasted patients with COPD. *Med Sci Sports Exerc* 2006; **38**(9)**:** 1543-52.

8. van Helvoort HA, Heijdra YF, Dekhuijzen PN. Systemic immunological response to exercise in patients with chronic obstructive pulmonary disease: what does it mean? *Respiration* 2006; **73**(2)**:** 255-64.

9. Rabinovich RA, Figueras M, Ardite E, Carbo N, Troosters T, Filella X *et al.* Increased tumour necrosis factor-alpha plasma levels during moderate-intensity exercise in COPD patients. *Eur Respir J* 2003; **21**(5)**:** 789-94.

10. Koechlin C, Maltais F, Saey D, Michaud A, LeBlanc P, Hayot M *et al.* Hypoxaemia enhances peripheral muscle oxidative stress in chronic obstructive pulmonary disease. *Thorax* 2005; **60**(10)**:** 834-41.

11. Swallow EB, Reyes D, Hopkinson NS, Man WD, Porcher R, Cetti EJ *et al.* Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 2007; **62**(2)**:** 115-20.

12. Barreiro E, Schols AM, Polkey MI, Galdiz JB, Gosker HR, Swallow EB *et al.* Cytokine profile in quadriceps muscles of patients with severe COPD. *Thorax* 2008; **63**(2)**:** 100-7.

13. Canavan J, Linton-Willoughby B, Garrod R. Acute Exercise Testing of COPD Patients: The Effect on Systemic Inflammatory Proteins. *Current Respiratory Medicine Reviews* 2011; **7:** 464-474.

14. Crul T, Spruit MA, Gayan-Ramirez G, Quarck R, Gosselink R, Troosters T *et al.* Markers of inflammation and disuse in vastus lateralis of chronic obstructive pulmonary disease patients. *Eur J Clin Invest* 2007; **37**(11)**:** 897-904.

15. Bruunsgaard H. Physical activity and modulation of systemic low-level inflammation. *J Leukoc Biol* 2005; **78**(4)**:** 819-35.

16. Petersen AM, Pedersen BK. The role of IL-6 in mediating the anti-inflammatory effects of exercise. *J Physiol Pharmacol* 2006; **57 Suppl 10:** 43-51.

17. van Helvoort HA, van de Pol MH, Heijdra YF, Dekhuijzen PN. Systemic inflammatory response to exhaustive exercise in patients with chronic obstructive pulmonary disease. *Respir Med* 2005; **99**(12)**:** 1555-67.

18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**(5)**:** 373-83.

19. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994; **47**(11)**:** 1245-51.

20. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; **186**(2)**:** 155-61.

21. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988; **93**(3)**:** 580-6.

22. Garrod R, Bestall JC, Paul EA, Wedzicha JA, Jones PW. Development and validation of a standardized measure of activity of daily living in patients with severe COPD: the London Chest Activity of Daily Living scale (LCADL). *Respir Med* 2000; **94**(6)**:** 589-96.

23. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**(6)**:** 361-70.

24. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; **145**(6)**:** 1321-7.

25. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A *et al.* Standardisation of spirometry. *Eur Respir J* 2005; **26**(2)**:** 319-38.

26. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F *et al.* Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; **26**(3)**:** 511-22.

27. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V *et al.* Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; **26**(4)**:** 720-35.

28. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993; **16:** 5-40.

29. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; **167**(2)**:** 211-77.

30. Videira PA, Amado IF, Crespo HJ, Alguero MC, Dall'Olio F, Cabral MG *et al.* Surface alpha 2-3- and alpha 2-6-sialylation of human monocytes and derived dendritic cells and its influence on endocytosis. *Glycoconj J* 2008; **25**(3)**:** 259-68.

31. Meijerink J, Mandigers C, van de Locht L, Tonnissen E, Goodsaid F, Raemaekers J. A novel method to compensate for different amplification efficiencies between patient DNA samples in quantitative real-time PCR. *J Mol Diagn* 2001; **3**(2)**:** 55-61.

32. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; **166**(1)**:** 111-7.

33. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA *et al.* The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; **350**(10)**:** 1005-12.

34. GOLD. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2015. Disponível em: http://www.goldcopd.org. Consultado a 12 setembro de 2015. In: *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*, 2015.

35. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003; **107**(11)**:** 1514-9.

36. Garcia-Aymerich J, Gomez FP, Benet M, Farrero E, Basagana X, Gayete A *et al.* Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes. *Thorax* 2011; **66**(5)**:** 430-7.

37. Tamakoshi K, Yatsuya H, Kondo T, Hori Y, Ishikawa M, Zhang H *et al.* The metabolic syndrome is associated with elevated circulating C-reactive protein in healthy reference range, a systemic low-grade inflammatory state. *Int J Obes Relat Metab Disord* 2003; **27**(4)**:** 443-9.

38. Debigare R, Cote CH, Maltais F. Peripheral muscle wasting in chronic obstructive pulmonary disease. Clinical relevance and mechanisms. *Am J Respir Crit Care Med* 2001; **164**(9)**:** 1712-7.

39. Schols AM, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 1996; **51**(8)**:** 819-24.

40. Soler Cataluna JJ, Martinez Garcia MA. [Prognostic factors in chronic obstructive pulmonary disease]. *Arch Bronconeumol* 2007; **43**(12)**:** 680-91.

41. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005; **128**(4)**:** 2099-107.

42. Carreiro A, Santos J, Rodrigues F. Impact of comorbidities in pulmonary rehabilitation outcomes in patients with chronic obstructive pulmonary disease. *Rev Port Pneumol* 2013; **19**(3)**:** 106-13.

43. Areias V, Carreira S, Anciaes M, Pinto P, Barbara C. Co-morbidities in patients with gold stage 4 chronic obstructive pulmonary disease. *Rev Port Pneumol* 2014; **20**(1)**:** 5-11.

44. Sin DD, Man SF, Marciniuk DD, Ford G, FitzGerald M, Wong E *et al.* The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; **177**(11)**:** 1207-14.

45. Moldoveanu AI, Shephard RJ, Shek PN. Exercise elevates plasma levels but not gene expression of IL-1beta, IL-6, and TNF-alpha in blood mononuclear cells. *J Appl Physiol (1985)* 2000; **89**(4)**:** 1499-504.

46. Ostrowski K, Rohde T, Zacho M, Asp S, Pedersen BK. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. *J Physiol* 1998; **508 (Pt 3)**: 949-53.

47. Netea MG, Drenth JP, De Bont N, Hijmans A, Keuter M, Dharmana E *et al.* A semi-quantitative reverse transcriptase polymerase chain reaction method for measurement of MRNA for TNF-alpha and IL-1 beta in whole blood cultures: its application in typhoid fever and exentric exercise. *Cytokine* 1996; **8**(9)**:** 739-44.

48. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA* 2003; **289**(14)**:** 1785-91.

Supplementary material

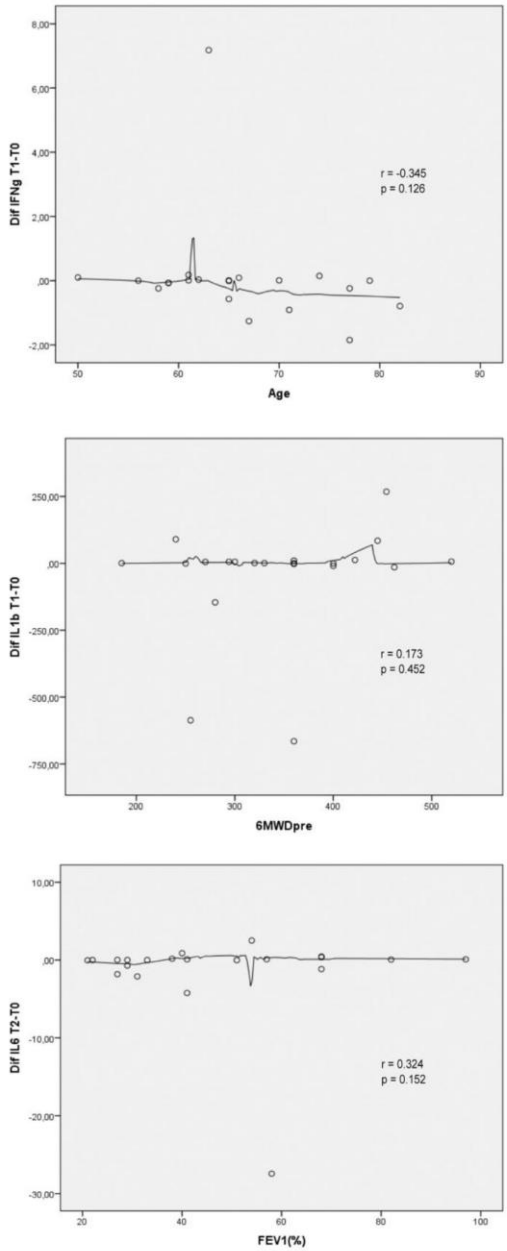

Figure 1a – Association between some patients' characteristics (age $_{years}$, $FEV_{1\ \%\ predicted}$ and 6MWD $_{meters}$) and some inflammatory biomarkers expression (mRNA IFNg $_{T1\text{-}T0}$, IL1b $_{T1\text{-}T0}$, and IL6 $_{T2\text{-}T0}$). r is the value of Spearman's correlation coefficient.

Table 1a - Median (P_{25}-P_{75}) of the mRNA inflammatory genes at rest in two consecutive days (T0 and C0).

	T0	C0	T0 vs C0 p
IFNg	0.16 (0.04-1.57)	0.03 (0.02-0.06)	0.180*
IL1b	15.46 (6.42-266.69)	7.26 (3.76-7.84)	0.754*
IL6	0.33 (0.11-2.81)	0.07 (0.02-0.34)	0.563**
IL8	1.82 (0.97-69.57)	0.86 (0.50-1.09)	0.754*
TNFa	2.99 (2.55-47.00)	2.03 (1.60-2.42)	0.232**
TGFb	199.71 (64.86-5462.36)	63.88 (58.29-72.56)	1.000*
iNOS	0.03 (0.01-0.29)	0.02 (0.01-0.05)	0.727*

*Sign Test
** Exact Wilcoxon Signed Ranks Test

Table 2a – Association between cardiovascular comorbidity and mRNA gene expression. *Higher inflammatory expression in patients with no cardiovascular comorbidity.

		p
IFNg	T1-T0	0.008*
	T2-T0	0.205
IL1b	T1-T0	0.006*
	T2-T0	0.791
IL6	T1-T0	0.199
	T2-T0	0.689
IL8	T1-T0	0.519
	T2-T0	0.957
TNFa	T1-T0	0.055*
	T2-T0	0.023*
TGFb	T1-T0	0.302
	T2-T0	0.302
iNOS	T1-T0	0.011*
	T2-T0	0.096*

Mann-Whitney U

ESTUDOS 5 a 7

PROGRAMAS DE REABILITAÇÃO RESPIRATÓRIA EM DOENTES COM DPOC:

REABILITAÇÃO SEGUNDO AS CATEGORIAS A, B, C E D

IMPACTO DAS COMORBILIDADES NOS RESULTADOS DA REABILITAÇÃO RESPIRATÓRIA

EFEITO DE DIFERENTES INTENSIDADES DE TREINO NOS RESULTADOS CENTRADOS NO DOENTE

PULMONARY REHABILITATION IN COPD ACCORDING TO GOLD CATEGORIES A, B, C AND D – A PROSPECTIVE COHORT STUDY.

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Abstract

Background

Pulmonary Rehabilitation (PR) programs are a mainstay for treatment in Chronic Obstructive Pulmonary Disease (COPD). Lung function impairment alone does not predict beneficial effects of PR. The new COPD categories A, B, C, and D take into account assessment of symptoms as dyspnea and exacerbations which may be important indications for PR. This study evaluates the effect of PR on exercise capacity, symptoms and health status in different COPD categories.

Methods

COPD subjects referred for PR were classified into COPD categories A, B, C and D. Exercise capacity measured by 6-minute walking distance (6MWD) and constant work rate (CWR) at 80% of peak work rate, symptoms measured by Mahler's index and health status measured by Saint George's Respiratory Questionnaire (SGRQ) were compared before and after PR programs for each COPD category. Changes were tested for minimum clinical important difference (MCID) and statistical significance ($P < .05$).

Results

167 subjects were included (16% in COPD category A, 12% category B, 31% category C and 41% category D). Groups were homogenous in age, Body Mass Index, smoking pack-years and comorbidities. Significant improvements in most outcomes were found in all COPD categories. All COPD categories improved exercise capacity (6MWD and CWR). Categories A and C had more pronounced improvements in 6MWD than categories B and D. Symptoms (Mahler's index) also improved significantly in categories A and C, while change was not significant in categories B and D. Global health status (SGRQ) improved significantly for all COPD categories. Despite these differences, the proportion of patients who achieved MCID in each outcome was similar in all categories.

Conclusion

This study demonstrates that patients in all COPD categories may improve exercise capacity, symptoms and health-status with PR programs and COPD categories alone may not be sufficient to discriminate which patients may benefit most from them.

Key words: *Pulmonary Rehabilitation, COPD, COPD categories, Quality of Life, 6-minute walking distance, Constant work rate, Saint George's Respiratory questionnaire, Mahler's index.*

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a debilitating disease commonly causing varying degrees of dyspnea, deconditioning and difficulties in daily activities [1, 2]. Although primarily a respiratory condition with increased work of breathing, the systemic effects of COPD result in loss of skeletal muscle mass and function, contributing to muscle weakness. Skeletal muscle atrophy is a clear negative prognostic factor [3] and loss in quadriceps strength has been shown to predict mortality in COPD [4]. Individuals with COPD also have multiple risk factors for cardiovascular disease including smoking, physical inactivity and metabolic disorders [5] and psychological wellbeing is also affected by physical and social impairments.

Pulmonary Rehabilitation (PR) programs are considered to be a mainstay of treatment in COPD [6] and have clearly demonstrated to reduce dyspnea, increase exercise capacity and improve quality of life [7-9]. The American Thoracic and European Respiratory Societies (ATS/ERS) currently recommend PR programs to be comprehensive interventions with patient-tailored therapies that include exercise training, self-management education, and behavior change, designed to improve physical and psychological condition [2]. Although PR programs are costly and time consuming with interventions that include comprehensive patient screening and treatment by a specialized team, studies have demonstrated their cost-effectiveness in moderate to severe COPD [10]. It is important to quantify the success of such programs and determine which participants benefit most from them.

PR programs traditionally enrolled individuals with severe COPD, persistent symptoms or dyspnea as measured by the modified Medical Research Council breathlessness scale (mMRC) $\geq$ 2 (or MRC $\geq$ 3), according to the British Thoracic Society (BTS) and ATS/ERS guidelines [2, 11]. However, this paradigm is changing as increasing data suggests that patients with less severe disease and less symptoms also improve significantly across several outcomes [2]. Individuals with mMRC scale 1 and 2 have shown to improving exercise performance and health status as much as individuals with higher mMRC scores [12-15]. PR programs for mild COPD have also been successful with similar improvements in exercise capacity, quality of life scores and symptoms as in more severe COPD [16, 17].

Evidence has shown that degree of lung impairment alone (assessed by spirometry) is poorly correlated with exercise capacity [12, 18] and health status [19]. Similarly, lung function alone does not predict beneficial effects of PR programs neither can it be used as a sensitive outcome of intervention success [2].

According to current guidelines [1], COPD is classified into categories A, B, C and D, which take into account clinical assessment of symptoms as dyspnea and exacerbations, as well as lung function. COPD patients with Forced Expiratory Volume in 1 second (FEV_1) >50% and less than two respiratory exacerbations in the previous year and no hospital stays for respiratory exacerbations are classified as COPD categories A and B. Patients with either FEV_1 <50% or two or more respiratory exacerbations or one hospital stay due to a respiratory exacerbation in the previous year are classified as COPD categories C and D. The presence of symptoms, as measured by mMRC score $\geq$ 2 or the COPD Assessment Test (CAT) $\geq$ 10 indicates categories B or D. This classification reflects functional impairments that may be important indicators for rehabilitation programs and may support patient referral to PR Units. The aim of this study was to evaluate the effects of PR on exercise capacity, symptoms and health status in subjects of different COPD categories.

Methods

Study Design and Participants

This was a prospective cohort study. Individuals with COPD referred to the outpatient PR Unit of Pulido Valente Hospital were examined by a Pulmonologist and those meeting the inclusion and exclusion criteria were recruited consecutively for a full PR program.

Recruited subjects had post-bronchodilator results on most recent spirometry of FEV1/FVC <0.7 and had a history of smoking habits or clinical equivalent. All individuals had their therapy optimized and were clinically stable, defined as no change in dyspnea, cough or sputum beyond everyday variability, or requirement of antibiotic therapy in the preceding month. Subjects were classified into GOLD COPD categories A, B, C and D [1], according to the modified Medical

Research Council (mMRC) breathlessness scale, post-bronchodilator FEV_1 and number of exacerbations in the previous year, for statistical analysis.

Subjects were excluded from the study if they had unstable cardiac disease, severe orthopedic disease or any sensory or cognitive impairment.

Subjects were willing and able to participate in a hospital-based program and gave written, informed consent prior to baseline measurements to participate in the PR program and for collection of personal data for research purposes. The hospital's Ethics committee and administration board approved the trial conduction (IRB:DIRCLIN-20141222-479/2014) and all data was processed anonymously according to the institution's privacy policy.

The outpatient Pulmonary Rehabilitation program

The PR program was multidisciplinary, including pulmonologists, dedicated physiotherapists and nurses, nutritionists and psychologists. Subjects attended the PR unit thrice weekly. After an initial phase for education and adaptation to exercise equipment, individuals were assessed for a peak work rate (peakWR) on an initial incremental exercise test on bicycle ergometer or treadmill. PR programs had an 8 to 12-week duration.

Individually prescribed training programs included 1) Aerobic exercise training on treadmill or bicycle at a target intensity of 60 to 80% of peakWR; 2) Peripheral muscle exercises by circuit training on various strength equipment for abdominal, upper and lower limb exercises and weight lifting; and 3) Breathing control and sputum clearance techniques, according to patients' needs. These activities were supervised by physiotherapists. Subjects already using home ambulatory oxygen supplementation were provided with oxygen for exercise training purposes. Subjects who did not use ambulatory oxygen were not provided with supplemental oxygen unless exercise itself resulted in desaturation with unacceptable degrees of dyspnea or fatigue objectively reversible with oxygen supply to achieve 90% of SpO_2.

Subjects were encouraged to apply a home-exercise routine as a way to enhance activity levels and improve activity of daily living efficacy. Throughout the PR program, subjects were engaged in individualized or group self-management sessions provided by a multidisciplinary

rehabilitation team. These sessions included education on correct use of respiratory medication and the importance of regular physical activity and smoking cessation, as well as identification of symptoms and signs of exacerbations. When required, psychologist, nutritionist counseling and social support were provided. During the PR program, subjects were encouraged to continue the various strategies they achieved at their home setting environment.

Data collection

Demographic information and the results of spirometry performed on subjects entering the program were collected. The mMRC scale uses a simple grading system to score a patient's dyspnea with a five-point scale, from 0 to 4. It was used as a discriminative tool to characterize the study population [20, 21].

The number of exacerbations in the year previous to the PR program was obtained from medical records based on the number of visits to the emergency department and hospital stays.

The BODE Index (Body Mass Index, airflow obstruction, dyspnea and exercise capacity) was calculated at baseline using values for Kg/m^2, % predicted FEV_1, mMRC and 6-minute walking distance in meters, respectively [22] and is a tool for predicting life expectancy of COPD patients.

Comorbidities were recorded and used to assess the COPD specific comorbidity index (COTE) which includes the comorbidities with most robust association with increased death (cancers, pulmonary fibrosis, atrial fibrillation/flutter, congestive heart failure, coronary artery disease, gastric/duodenal ulcers, liver cirrhosis, diabetes with neuropathy, and anxiety) [23].

Finally, the presence of respiratory failure was also recorded.

Outcome measures

Compliance to the PR program was assessed by determining the number of sessions that were attended by each subject. A minimum of 70% attendance was required for fulfilling the program. Those who failed to comply were considered dropouts.

The success of the PR program was evaluated by assessing the improvement in four main outcomes measured at baseline and at the end of the PR program.

Exercise capacity was measured through the 6-minute walking distance (6MWD), according to ATS guidelines [24], on a 30m walking course where subjects were instructed to walk as far as possible for six minutes, and the Constant Work Rate Endurance test (CWR), measured in minutes on bicycle ergometer or treadmill at 80% of the peakWR [25, 26]. Minimum clinical important difference (MCID) was defined at 35m for the 6MWD, according to distribution- and anchor-based methods [27, 28] and 85 seconds for the CWR, according to an anchor-based method with a 5-point Likert scale [29].

Symptom control was assessed by the Mahler's Baseline and Transitional Dyspnea Index (BDI/TDI) [30], a scale of five grades, scored 0 to 4, for each of the categories: functional impairment, magnitude of task and magnitude of effort. Scores ranged from -9 to +9, with positive scores meaning improvement in dyspnea. MCID was defined as a change of at least 1 point.

Health status was assessed by Saint George's Respiratory Questionnaire (SGRQ), a 76 weighted-item questionnaire in which results are expressed for symptoms, activity and impacts on daily life. An integrated total score reflects health impairment where zero indicates no impairment and 100 represents maximum impairment. A variation of at least 4 points in global score was considered for MCID [31, 32].

Statistical analysis

An exploratory analysis was carried out for all variables. Categorical data were presented as frequencies (percentages), and continuous variables as mean and standard deviation (SD) or median and inter-quartile range (25^{th} percentile - 75^{th} percentile), as appropriate.

Baseline characteristics between COPD categories were compared using Chi-square test or Fisher's exact test, and Kruskal-Wallis test, as required.

To take into account the correlation structure between longitudinal measures, generalized estimating equations with an exchangeable correlation structure, were used to assess intervention effect on 6MWD, CWR, BDI/TDI, and SGRQ values.

Regarding the proportion of subjects that attained a MCID in 6MWD, CWR, BDI/TDI, and SGRQ outcomes, the odds ratios of each COPD category (considering category D as reference) were obtained by logistic regression models, as well as corresponding 95% confidence intervals. Several potential confounders such as age, gender, BMI, and COTE were also considered in all the regression analyses.

The level of significance was P=.05. Data analysis was performed using the software SPSS 22.0 (SPSS for Windows, Rel. 22.0.1. 2013. SPSS Inc., Chicago, Il, EUA) and Stata (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.)

Results

167 subjects were included in this study. 16% were classified in COPD category A, 12% in COPD category B, 31% in COPD category C and 41% in COPD category D (Table 1). Most individuals (94%) had a past or current smoking status. There were no significant differences in age, BMI and smoking pack years between groups. Male gender was more prevalent in COPD categories C and D than in COPD categories A and B (P = .001). Spirometry results differed between groups ($P \leq .001$).

Table 1 Characteristics of study participants at baseline.

		Total n = 167	COPD A n = 27	COPD B n = 20	COPD C n = 52	COPD D n = 68	*P*
Gender, male	**n (%)**	137 (82.0%)	18 (66.6%)	13 (65.0%)	50 (96.2%)	56 (82.4%)	.001 *
Age	**(years)**	65.2 (9.5)	66.9 (10.9)	64.1 (11.9)	65.7 (8.5)	64.5 (9.0)	.58 †
BMI	**(Kg/m^2)**	26.2 (4.8)	26.7 (4.8)	28.1 (5.3)	25.7 (4.1)	25.7 (4.9)	.26 †
Smoking pack-years		50 (40-73)	50 (44-75)	50 (39-90)	51 (38-70)	54 (40-74)	.93 †
BODE		3 (2-5)	1 (0-2)	2 (1-3)	3 (2-4)	5 (4-6)	<.001 †
COTE		.0	.0 (.0-2.0)	.0 (.0-1.0)	.0 (.0-1.0)	1 (.0-2.0)	.47 †
Hypoxemic RF	**n(%)**	66 (39.5%)	13 (48.1%)	10 (50.0%)	15 (28.8%)	28 (41.2%)	.23 ‡
Hypercapnic RF	**n(%)**	42 (25.1%)	1 (3.7%)	2 (10.0%)	12 (23.1%)	27 (39.7%)	.001 ‡
FVC	**(L)**	2.7 (2.3-3.5)	3.3 (2.6-3.9)	2.9 (2.7-3.4)	2.9 (2.3-3.5)	2.4 (2.1-3.0)	.001 †
	(%)	81.0 (69-102)	94.0 (84-107)	96.0 (85-108)	81.0 (64-93)	74.0 (62-85)	<.001 †
FEV_1	**(L)**	1.1 (0.9-1.5)	1.7 (1.3-2.1)	1.5 (1.2-1.4)	1.1 (0.9-1.4)	.9 (0.7-1.82)	<.001 †
	(%)	42.0 (33-57)	65.0 (55-74.5)	62.0 (51-82)	40.5 (32-48)	34.0 (30-41)	<.001 †
FEV_1/FVC	**(%)**	43.0 (34-53)	52.0 (49-59)	51.0 (44-61)	42.0 (34-49)	36.0 (32-47)	<.001 †
6MWD	**(m)**	330 (280-442.5)	422 (328-490)	355 (318-475)	360 (304-453)	290 (245-374)	<.001 †
CWR	**(min)**	5 (3-12)	5 (3-13)	7 (3-15)	5 (3-15)	5 (3-10)	.89 †
Mahler BDI		7 (6-9)	8 (6.8-10)	8.0 (6-9)	8 (6-10)	6 (5-8)	.001 †
SGRQ		45.6 (17.3)	38.1 (14.7)	46.2 (16.1)	37.3 (13.4)	56.5 (16.2)	<.001 †
Dropouts	**n (%)**	35 (21.0%)	1 (3.7%)	4 (20.0%)	13 (25.0%)	17 (25.0%)	.075 *

Data presented as mean (SD) or median (P25-P75) or n (%).
Abbreviations: COPD = Chronic Obstructive Lung Disease; BMI = Body Mass Index; BODE = BMI, airflow obstruction, dyspnea and exercise capacity index; COTE = COPD Comorbidity Test; RF = Respiratory Failure; FVC = Forced Vital Capacity; FEV_1 = Forced Expiratory Volume in 1 second; 6MWD = 6 Minute Walking Distance; MCID = Minimum Clinical Important Difference; CWR = Constant Work Rate; SGRQ = St. George's Respiratory Questionnaire; BDI = Baseline Dyspnea Index.* Fisher's exact test, † Kruskal-Wallis test, ‡ Chi Square test

BODE was significantly different between categories, with higher score in category D ($P < .001$).

Most subjects (91%) had cardiovascular comorbidities, of which arterial hypertension was the most frequently recorded (49%), followed by ischemic heart disease (13%), heart failure (9.5%), arrhythmias (9.5%) and *cor pulmonale* (9%). 19% had architectural distortion of the lung from past pulmonary tuberculosis and 28% had some degree of bronchiectasis although these were not considered the patients' primary lung disease. Alpha-1 antitrypsin deficiency was found in 6.6% subjects. Obstructive Sleep Apnea-Hypopnea syndrome (OSAH) was found in 14% subjects.

Diabetes mellitus was found in 13%, obesity in 12.6% and hypercholesterolemia in 17% of subjects. Orthopedic disorders were present in 16%. Depression or anxiety were reported in 7% of individuals, as were thyroid disorders. Only the occurrence of hypercholesterolemia was found to be different between categories, being more prevalent in categories A, B and C, (P = .030).

COTE index was not significantly different between categories (P = .47). Hypoxemic respiratory failure, found in a total of 39.5% of subjects, was equally present across all categories (P = .23). However, hypercapnic respiratory failure, found in 25.1% of subjects, was significantly more frequent in category D and less frequent in category A (P = .001) (Table 1).

Individuals in COPD category A were found to be referred to the Rehabilitation Unit due to at least one of the following: hypoxemic respiratory failure or desaturation on exertion (74%), persistent productive cough (15%), obesity (15%), malnutrition (7%) and one subject due to hypercapnic respiratory failure.

A total of 132 subjects completed the PR program at a mean 73% (SD = 11.5%) of peakWR. Dropouts were due to non-compliance and unwillingness to complete the program (9 cases), learning difficulties or psychological impairment to progress in the program (6 cases), COPD exacerbations that forced interruption (5 cases), familial or economic issues (3 cases), skeletal muscle impairment (3 cases), diagnosis of other non-related diseases during the time undertaking PR that forced interruption (2 cases) and cardiovascular complications including tachyarrhythmia (4 cases), one deep vein thrombosis and one arterial ischemia of the lower limbs.

One death was recorded during the study period which occurred during night sleep in a subject with coronary artery disease and past history of myocardial infarction. Death was attributed to myocardial infarction. The percentage of dropouts was not significantly different between COPD categories (P = .075).

Dropouts were similar in age (P = .33), gender (P = .46), BMI (P = .055), smoking habits (P = .62), mMRC score (P = .18), and airflow limitation as %predicted FEV_1 (P = .052) comparing to those subjects who fulfilled the PR program.

Outcomes

Baseline measurements for the median 6MWD were significantly different between categories A, B, C and D ($P < .001$) where COPD category A subjects fared better and COPD category D subjects fared significantly worse. CWR was found to be similar between all COPD categories at baseline ($P = .89$). Mahler's BDI evidenced a lower score in category D ($P = .001$). Similarly, values for quality of life measured with SGRQ were found to be significantly worse at baseline in COPD categories B and D ($P < .001$) as shown in Table 1.

As a whole, subjects with COPD had a significant improvement in all end-points after Pulmonary Rehabilitation. Significant differences in most outcomes were also found within each COPD category.

The 6MWD values improved significantly in all COPD categories (Figure 1). For comparison between different categories, generalized estimated equations were calculated using COPD category D as reference. These showed significant differences in median improvement in 6MWD between categories, with categories A and C having more pronounced improvement after PR programs. We also found that the variables of age and COTE index had a negative impact on change in 6MWD (Table 2). The proportion of subjects with an $\geq$ 35 m (MCID) increase in 6MWD was 56.1%. Logistic regression analysis showed no difference in the number of subjects who achieved MCID in different COPD categories (Table 3).

Table 2 Improvement in outcomes stratified according to COPD category, by generalized estimating equations (see explanation in the text).

6MWD (m)	**Regression coefficient estimate**	**95% C.I.**	***P***
COPD A	127.34	(85.63 , 169.06)	<.001
COPD B	51.19	(3.32 , 99.05)	.036
COPD C	70.40	(36.16 , 99.05)	<.001
All categories	51.33	(40.98 , 61.68)	<.001
Age	- 1.72	(-3.24 , -.19)	.027
COTE	- 13.18	(-21.34 , -5.02)	.002
CWR (min)			
COPD A	1.70	(-4.04 , 7.44)	.56
COPD B	2.21	(-4.65 , 9.08)	.53
COPD C	2.49	(-2.46 , 7.44)	.32
All categories	8.47	(6.60 , 10.34)	<.001
Age	- .28	(-.48 , -.07)	.009
BDI/TDI			
COPD A	3.44	(2.07 , 4.82)	<.001
COPD B	1.87	(.22 , 3.52)	.026
COPD C	2.81	(1.58 , 4.04)	<.001
All categories	1.04	(.39 , 1.69)	.002
SGRQ			
COPD A	- 19.11	(-25.94 , -12.28)	<.001
COPD B	-12.06	(-20.54 , -3.58)	.005
COPD C	-19.27	(-25.17 , -13.37)	<.001
All categories	-8.08	(-10.60 , -5.55)	<.001

Abbreviations: COPD = Chronic Obstructive Lung Disease; 6MWD = 6 Minute Walking Distance; CWR = Constant Work Rate; BDI/TDI = Baseline and Transitional Dyspnea Index; SGRQ = St. George's Respiratory Questionnaire.

Table 3 Odds ratios for attaining MCID in the studied outcomes, stratified according to COPD category (considering category D as reference), by logistic regression models.

6MWD (m)	**OR estimate**	**95% C.I.**	***P***
COPD A	1.60	(.61 , 4.18)	.337
COPD B	1.00	(.33 , 3.07)	>.99
COPD C	1.71	(.73 , 4.03)	.22
All categories			.553
CWR (min)			
COPD A	1.06	(.37 , 3.03)	.92
COPD B	1.69	(.47 , 6.14)	.43
COPD C	2.20	(.86 , 5.65)	.101
All categories			.35
BDI/TDI			
COPD A	2.73	(.99 , 7.54)	.052
COPD B	1.13	(.35 , 3.60)	.84
COPD C	2.02	(.84 , 4.87)	.12
All categories			.17
SGRQ			
COPD A	1.22	(.42 , 3.59)	.71
COPD B	1.14	(.28 , 4.58)	.85
COPD C	1.30	(.49 , 3.45)	.59
All categories			.96

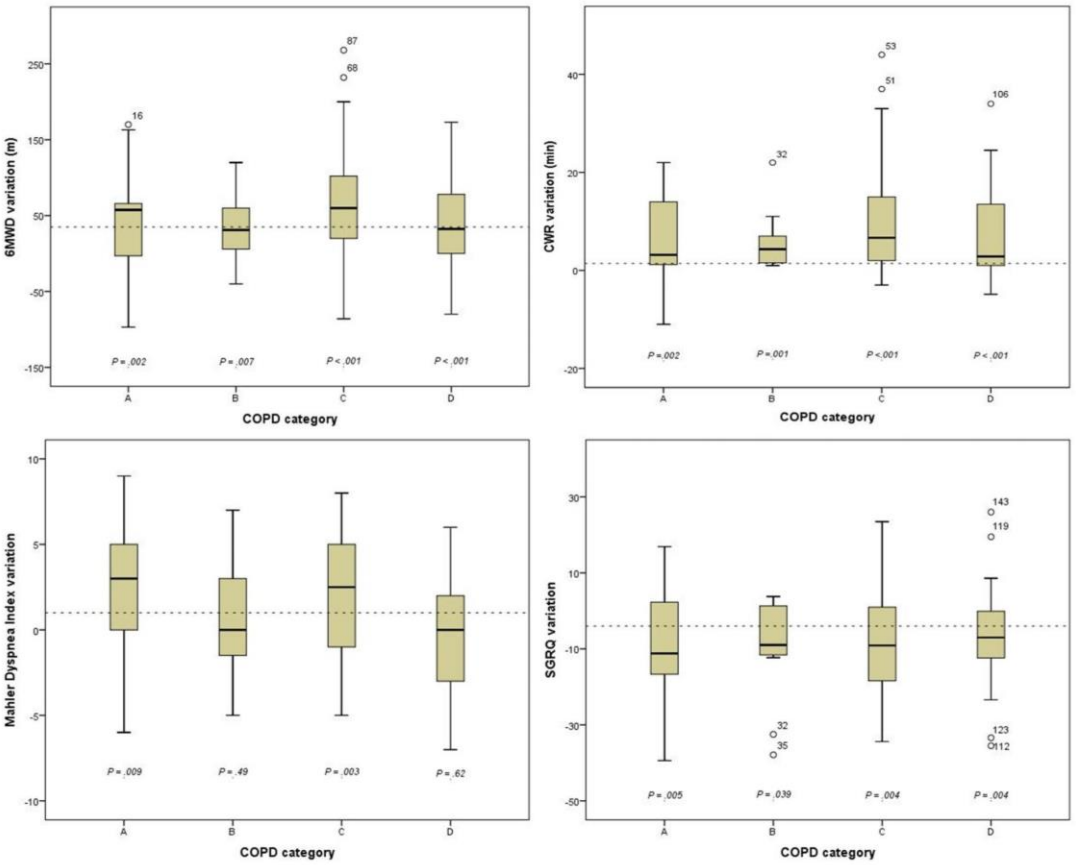
Abbreviations: COPD = Chronic Obstructive Lung Disease; 6MWD = 6 Minute Walking Distance; CWR = Constant Work Rate; BDI/TDI = Baseline and Transitional Dyspnea Index; SGRQ = St. George's Respiratory Questionnaire.

Exercise capacity, as measured by the CWR Endurance Test, evidenced significant improvements after the PR program. There was a highly significant improvement in CWR in all COPD categories (Figure 1). All categories showed a similar improvement in this outcome. Once again, age was found as a negative impact variable for CWR change (Table 2). 56.9% of subjects achieved a MCID of 85 seconds in CWR after PR. Logistic regression analysis showed that the proportion of subjects who achieved MCID was also similar in each COPD category (Table 3).

Regarding symptom control, as measured by Mahler's index, we found that COPD categories A and C improved significantly with the PR but there was no significant change in the BDI/TDI in COPD categories B and D (Figure 1). Generalized estimated equations also found that the effect of PR on Mahler's index was significantly different in categories A, B and C when compared with category D (Table 2). 54% of subjects had at least a one-point improvement in Mahler's index. The proportion of subjects that showed this improvement was similar between all categories, having logistic regression models showed only some evidence that category A subjects had more improvement that category D subjects. This was not significantly different, however (Table 3).

Finally, all COPD categories had a significant improvement in SGRQ scores with the PR program (Figure 1). There were significant differences in median improvement in this outcome in categories A, B and C when compared to category D (Table 2). 63.8% of subjects achieved MCID with a decrease of at least 4 points in SGRQ and the proportion of patients with this improvement was not significantly different between categories (Table 3).
By logistic regression analysis, age, gender, BMI and COTE didn´t show a significant association with the proportion of subjects that achieved MCID in each outcome.

Figure 1 Median improvement in the four outcomes after Pulmonary Rehabilitation in different COPD categories. **Up left** - 6-minute walking distance (6MWD). **Up right** - Constant Work Rate (CWR). **Bottom left** - Dyspnea measured by Mahler's Basal and Transitional Dyspnea Index. **Bottom right** - St. George's Respiratory Questionnaire (SGRQ). Draft line indicates MCID improvement for each outcome (see text for explanation)



Discussion

This study sheds new light in the referral of patients with COPD to PR programs and the beneficial effects that may be expected by these interventions. To the best of our knowledge, this is the first paper that evaluates the effects of Pulmonary Rehabilitation according to the most recent grading of COPD into categories A to D. The results confirm the benefits of PR across all categories of COPD.

It has been widely demonstrated how intensive, multidisciplinary PR programs with focus on aerobic, muscle strength and breathing control exercises as well as self-management education are important to produce positive effects on COPD. This PR program complied with these requisites. The overall improvements recorded in these groups were similar to other studies [33-35].

The new grading of COPD takes into account not only spirometric obstruction but also symptoms and exacerbations. Previous studies have assessed if these variables predict greater benefit from PR programs. Success in exercise tolerance has been reported by Evans et al. in 58% patients as well as Garrod et al. with similar results in patients with different degrees of dyspnea in the MRC scale [12, 13]. Man et al. also found that patients with mMRC scale 1 and 2 improved their exercise performance and health status as much as patients with higher mMRC scores [14].

Although it has been accepted that patients with moderate COPD may benefit from PR programs, there is scarce evidence on the success of PR in mild COPD. However, in Jacome et al. review [16] two retrospective and one randomized study have shown that patients with mild COPD improve 6MWD, quality of life scores and symptoms with PR. Berry et al. [17] also found that patients in spirometric stages I, II and III all had similar improvements in exercise tolerance outcomes and CRQ domains of dyspnea and fatigue after PR programs.

In the present study, subjects were graded into the four COPD categories by the mMRC scale (categories A and C had mMRC scale $\leq$1), airflow limitation and number of exacerbations, and we also found that all benefitted from the PR program.

Four main outcomes were used to assess PR program success in this study. The exercise performance outcomes (6MWD and CWR) have been validated as sensitive outcomes for PR

programs [36], and Mahler's Baseline and Transitional Dyspnea Index has been shown to be a sensitive tool to detect moderate changes in dyspnea [36, 37] and assess the impact of dyspnea on activities of daily living. SGRQ is a subjective measure of PR success and in previous studies [15], improvement in this score was more common than in objective measures such as 6MWD. This is of great importance because one of the primary goals of PR is to relieve symptoms and enhance tolerance to daily activities [7].

Regarding the change in functional capacity, the present study showed that subjects in categories A and C had greater improvement in 6MWD. These results might be due to lower levels of baseline dyspnea in these categories compared to categories B and D. On the other hand, CWR, which markedly improved in all categories, was found to have similar variations in all of them, probably due to the nature of this test which is measured according to each subjects' personal best (80% of peak work rate).

Regarding the impact of symptoms in daily activities, we found differences between groups, with categories A and C having achieved greater improvements in BDI/TDI. We assume that these patients are less symptomatic and therefore usually less limited in their activities. This may also explain our findings in the 6MWD. The SGRQ was another very sensitive outcome for the PR program in all categories, with A, B and C having had a more pronounced effect.

This study highlights that in spite of the amplitude of the outcomes with PR program, the proportion of patients that achieve MCID is similar across all COPD categories. This finding is utmost relevance as it reflects the real purpose of PR program referral.

Furthermore, all COPD categories, including the less severe patients, have shown to benefit from PR programs and should be considered for these interventions. In our study, category A subjects represent a subset of patients that had been referred for hospital-based PR due to at least one of various motives that are not ubiquitous to all patients in this category (hypoxemic respiratory failure or desaturation on exertion, persistent productive cough, obesity or malnutrition and also one case of hypercapnic respiratory failure). These complicating factors were found in an unexpectedly high proportion of subjects in this category.

Mean FEV_1 in this group was 65%, but varied from 50 to 97%. This also reflects the clinical heterogeneity of patients in COPD category A. Although some outpatient-based studies did not

find consistent improvements in quality-of-life dimensions in less symptomatic individuals [38], the current study took place in a hospital setting where these patients had the above complicating factors, thus having more scope for improvement, and where adherence rates are probably higher than in community settings.

We also found that category A subjects in this study didn't differ significantly to other categories in regards to prevalence of comorbidities. Cardiovascular diseases were highly prevalent in all subjects and no significant differences were found between categories [39, 40]. This illustrates that this subset of COPD category A individuals had more than expected comorbidities and thus were more prone to be selected for a PR program.

Recent data have suggested that COPD categories may not be sufficient to predict prognosis, disease progression or mortality and this may be partly due to the need to take into consideration other risk factors [41, 42]. We may argue that comorbidities may further enhance the need for a PR program in COPD and do not impair its potential benefits [43, 44].

This study has some limitations that should be addressed. This was not a randomized or controlled study and so cannot prevent patient inclusion bias. Nevertheless, it reflects a "real-world" hospital-based outpatient PR program, and all the referred individuals to PR program entered the study, with no other selection bias. This study assessed the short term impact of the PR program in different COPD categories. Further studies should be designed to search for long-term benefits of PR programs in each GOLD COPD category, such as the long-term impact in frequency and severity of exacerbations or in health-care use, as well as the adherence to life-style changes and home-exercise routine. It would also be interesting to find out if PR programs may result in COPD category shifts and if these shifts are short or long-term.

Finally, depression and anxiety were not considered as outcomes in this study. However, subjects were systematically assessed with Depression and Anxiety scales and if needed, received psychological counseling. Studies have shown that these interventions are important in the overall success of PR programs [45, 46] and further studies could assess their relationship in different COPD categories, and how they may influence other health status and symptoms outcomes.

Conclusion

Overall, this study further contributes to show how COPD categories on their own may not be sufficient to predict which patients might benefit most from PR programs. Individuals in all COPD categories may benefit from PR achieving both statistically and clinically meaningful improvements in exercise performance and health-related quality-of-life.

Multidisciplinary PR should be adopted as an integral part of management of patients with COPD, early in the course of the disease and should not exclude apparently less severe or less symptomatic subjects.

An individualized approach to COPD is important to identify characteristics and contributing factors such as symptoms, comorbidities or limitations to activities of daily living that increase the burden of the disease and cause further impairment on quality of life, but might be improved with interventions such as PR.

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References

1. GOLD. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2015. Available from: http://www.goldcopd.org.
2. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013;188(8):e13-64.
3. Decramer M, Gosselink R, Troosters T, Verschueren M, Evers G. Muscle weakness is related to utilization of health care resources in COPD patients. Eur Respir J 1997;10(2):417-423.
4. Swallow EB, Reyes D, Hopkinson NS, Man WD, Porcher R, Cetti EJ, et al. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. Thorax 2007;62(2):115-120.
5. Gale NS, Duckers JM, Enright S, Cockcroft JR, Shale DJ, Bolton CE. Does pulmonary rehabilitation address cardiovascular risk factors in patients with COPD? BMC Pulm Med 2011;11:20.
6. GOLD. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2008. Disponível em: http://www.goldcopd.org. Consultado a 12 setembro de 2015.
7. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2015;2:CD003793.
8. Lacasse Y, Wong E, Guyatt GH, King D, Cook DJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. Lancet 1996;348(9035):1115-1119.
9. Salman GF, Mosier MC, Beasley BW, Calkins DR. Rehabilitation for patients with chronic obstructive pulmonary disease: meta-analysis of randomized controlled trials. J Gen Intern Med 2003;18(3):213-221.
10. Hoogendoorn M, van Wetering CR, Schols AM, Rutten-van Molken MP. Is INTERdisciplinary COMmunity-based COPD management (INTERCOM) cost-effective? Eur Respir J 2010;35(1):79-87.
11. Bolton CE, Blakey JD, Morgan MD. The British Thoracic Society guideline on pulmonary rehabilitation in adults: your opinion is noted. Thorax 2013;69(4):388-389.
12. Evans RA, Singh SJ, Collier R, Williams JE, Morgan MD. Pulmonary rehabilitation is successful for COPD irrespective of MRC dyspnoea grade. Respir Med 2009;103(7):1070-1075.
13. Garrod R, Marshall J, Barley E, Jones PW. Predictors of success and failure in pulmonary rehabilitation. Eur Respir J 2006;27(4):788-794.
14. Man WD, Grant A, Hogg L, Moore J, Barker RD, Moxham J. Pulmonary rehabilitation in patients with MRC Dyspnoea Scale 2. Thorax 2011;66(3):263.

15. Scott AS, Baltzan MA, Fox J, Wolkove N. Success in pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. Can Respir J 2010;17(5):219-223.
16. Jacome C, Marques A. Pulmonary rehabilitation for mild COPD: a systematic review. Respir Care 2014;59(4):588-594.
17. Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. Am J Respir Crit Care Med 1999;160(4):1248-1253.
18. McGavin CR, Gupta SP, McHardy GJ. Twelve-minute walking test for assessing disability in chronic bronchitis. Br Med J 1976;1(6013):822-823.
19. Curtis JR, Deyo RA, Hudson LD. Pulmonary rehabilitation in chronic respiratory insufficiency. 7. Health-related quality of life among patients with chronic obstructive pulmonary disease. Thorax 1994;49(2):162-170.
20. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J 1959;2(5147):257-266.
21. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54(7):581-586.
22. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350(10):1005-1012.
23. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;186(2):155-161.
24. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166(1):111-117.
25. Vivodtzev I, Gagnon P, Pepin V, Saey D, Laviolette L, Brouillard C, et al. Physiological correlates of endurance time variability during constant-workrate cycling exercise in patients with COPD. PLoS One 2011;6(2):e17007.
26. Borel B, Provencher S, Saey D, Maltais F. Responsiveness of Various Exercise-Testing Protocols to Therapeutic Interventions in COPD. Pulm Med 2013;2013:410748.
27. Holland AE, Nici L. The return of the minimum clinically important difference for 6-minute-walk distance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187(4):335-336.
28. Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schunemann HJ. Interpretation of treatment changes in 6-minute walk distance in patients with COPD. Eur Respir J 2008;32(3):637-643.
29. Puente-Maestu L, Villar F, de Miguel J, Stringer WW, Sanz P, Sanz ML, et al. Clinical relevance of constant power exercise duration changes in COPD. Eur Respir J 2009;34(2):340-345.
30. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 1984;85(6):751-758.
31. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002;19(3):398-404.

32. Ringbaek T, Martinez G, Lange P. A comparison of the assessment of quality of life with CAT, CCQ, and SGRQ in COPD patients participating in pulmonary rehabilitation. COPD 2012;9(1):12-15.
33. Barakat S, Michele G, George P, Nicole V, Guy A. Outpatient pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2008;3(1):155-162.
34. van Wetering CR, Hoogendoorn M, Mol SJ, Rutten-van Molken MP, Schols AM. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. Thorax 2010;65(1):7-13.
35. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet 2000;355(9201):362-368.
36. de Torres JP, Pinto-Plata V, Ingenito E, Bagley P, Gray A, Berger R, et al. Power of outcome measurements to detect clinically significant changes in pulmonary rehabilitation of patients with COPD. Chest 2002;121(4):1092-1098.
37. Jones P, Lareau S, Mahler DA. Measuring the effects of COPD on the patient. Respir Med 2005;99 Suppl B:S11-18.
38. Roman M, Larraz C, Gomez A, Ripoll J, Mir I, Miranda EZ, et al. Efficacy of pulmonary rehabilitation in patients with moderate chronic obstructive pulmonary disease: a randomized controlled trial. BMC Fam Pract 2013;14:21.
39. Agusti A, Edwards LD, Celli B, Macnee W, Calverley PM, Mullerova H, et al. Characteristics, stability and outcomes of the 2011 GOLD COPD groups in the ECLIPSE cohort. Eur Respir J 2013;42(3):636-646.
40. Boland MR, Tsiachristas A, Kruis AL, Chavannes NH, Rutten-van Molken MP. Are GOLD ABCD groups better associated with health status and costs than GOLD 1234 grades? A cross-sectional study. Prim Care Respir J 2014;23(1):30-37.
41. Soriano JB, Alfageme I, Almagro P, Casanova C, Esteban C, Soler-Cataluna JJ, et al. Distribution and prognostic validity of the new Global Initiative for Chronic Obstructive Lung Disease grading classification. Chest 2013;143(3):694-702.
42. Soriano JB, Rodriguez MR. A golden goal in 2010, and another GOLD in 2014 in primary care, or vice versa. Prim Care Respir J 2014;23(1):5-6.
43. Franssen FM, Rochester CL. Comorbidities in patients with COPD and pulmonary rehabilitation: do they matter? Eur Respir Rev 2014;23(131):131-141.
44. Carreiro A, Santos J, Rodrigues F. Impact of comorbidities in pulmonary rehabilitation outcomes in patients with chronic obstructive pulmonary disease. Rev Port Pneumol 2013;19(3):106-113.
45. Paz-Diaz H, Montes de Oca M, Lopez JM, Celli BR. Pulmonary rehabilitation improves depression, anxiety, dyspnea and health status in patients with COPD. Am J Phys Med Rehabil 2007;86(1):30-36.
46. de Godoy DV, de Godoy RF. A randomized controlled trial of the effect of psychotherapy on anxiety and depression in chronic obstructive pulmonary disease. Arch Phys Med Rehabil 2003;84(8):1154-1157.

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ARTIGO ORIGINAL

Impacto das comorbilidades num programa de reabilitação respiratória em doentes com doença pulmonar obstrutiva crónica

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PALAVRAS-CHAVE
Reabilitação respiratória;
Exercício;
Comorbilidades;
Doença pulmonar obstrutiva crónica

Resumo
Introdução: A doença pulmonar obstrutiva crónica (DPOC) apresenta um impacto crescente a nível mundial. Devido ao seu impacto sistémico, e porque constitui um importante fator de risco para outras comorbilidades crónicas, a DPOC não pode já ser considerada uma doença com envolvimento exclusivamente pulmonar.
Objetivo: Determinar a frequência das comorbilidades em doentes com DPOC que são submetidos a um programa de reabilitação respiratória (PRR) e avaliar a influência das suas características basais, bem como das suas comorbilidades nos resultados do PRR.
Métodos: O presente estudo incluiu todos os doentes com DPOC que foram admitidos na Unidade de Reabilitação Respiratória para um PRR. A resposta à reabilitação respiratória (RR) foi avaliada pela melhoria na tolerância ao exercício (prova de marcha de 6 min), na dispneia (índice de dispneia de Mahler) e na qualidade de vida relacionada com a saúde (questionário respiratório de St. George).
Resultados: Foram incluídos 114 doentes com DPOC. A maioria dos doentes (96,5%) tinha pelo menos uma comorbilidade. As doenças metabólicas (71,1%), as doenças cardiovasculares (67,5%), outras patologias respiratórias (57,9%) e a ansiedade/depressão (21,1%) foram as mais prevalentes. Apresentaram melhoria na tolerância ao exercício, na qualidade de vida e na dispneia, respetivamente, 64,9, 64,9 e 51,1% dos doentes.
A globalidade dos resultados foi semelhante em todos os estadios da DPOC e em todos os subgrupos de comorbilidades. A análise por regressão logística demonstrou que a insuficiência respiratória e a doença coronária influenciaram negativamente a melhoria na qualidade de vida relacionada com a saúde, e que a ansiedade/depressão se relacionou com uma melhoria menos acentuada da dispneia.
Conclusão: A RR proporcionou melhoria nos doentes de todos os subgrupos de comorbilidades, salientando o papel fundamental do treino de exercício na reabilitação das doenças crónicas

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associadas à DPOC. Por outro lado, a presença de comorbilidades em doentes com DPOC, se clinicamente controladas, não deve impedir a sua inclusão na RR.

KEYWORDS
Pulmonary rehabilitation;
Exercise;
Comorbidities;
Chronic obstructive pulmonary disease

Impact of comorbidities in pulmonary rehabilitation outcomes in patients with chronic obstructive pulmonary disease

Abstract
Background: Chronic Obstructive Pulmonary Disease (COPD) represents an increasing burden worldwide. COPD can no longer be considered a disease which only involves the lungs, its systemic consequences make it an important risk factor for other chronic comorbidities.
Aim: To determine the frequency of comorbidities in patients with COPD undergoing a pulmonary rehabilitation program (PRP) and to evaluate the influence of baseline characteristics as well as comorbidities on the outcomes of PRP.
Methods: The present study included all COPD patients that were admitted to a PRP in our unit. The response to PR was measured by the improvement in exercise tolerance (6 minute walk test), dyspnea (Mahler's Dyspnea Index) and health status (St. George's Respiratory Questionnaire).
Results: 114 patients with COPD were included. Most patients (96,5%) had at least one comorbidity. Metabolic diseases (71.1%), cardiovascular diseases (67.5%), other respiratory conditions (57.9%) and anxiety/depression (21.1%) were the most prevalent ones. 64.9%, 64.9% and 51.1% of the patients improved in terms of exercise tolerance, quality of life and dyspnea, respectively.
The overall results were similar in all levels of the disease and in all comorbid subgroups. Logistic regression analysis showed that respiratory failure and ischemic heart disease negatively influenced improvement in health status and anxiety/depression predicted lower improvement in dyspnea.
Conclusion: PR was associated with improvements in all comorbid subgroups of patients, underlining the important role of exercise training in rehabilitation of those chronic diseases associated with COPD. On the other hand, the presence of comorbidities in COPD patients, if clinically controlled, should not preclude access to PR.

Introdução

A doença pulmonar obstrutiva crónica (DPOC) é uma doença prevenível e tratável, embora continue a aumentar em todo o mundo[1]. Este aumento é atribuído, entre outros fatores, ao fumo do tabaco, principalmente nas mulheres, e ao envelhecimento geral da população[2]. A OMS prevê que a DPOC constitua a 3.ª principal causa de mortalidade no mundo em 2030[3]. As exacerbações e as comorbilidades contribuem para a gravidade individual da doença[1].

A DPOC não afeta exclusivamente os pulmões, sendo uma doença sistémica mais complexa, com efeitos extrapulmonares significativos que contribuem para a sua gravidade, e está associada a outras doenças crónicas[4–6]. Estima-se que cerca de 2 terços dos doentes com DPOC tenham uma ou 2 comorbilidades[7]. A hipertensão arterial (HTA), a diabetes mellitus, a doença coronária, a insuficiência cardíaca, as infeções respiratórias e o cancro do pulmão são as comorbilidades mais frequentemente descritas em associação com a DPOC[5]. Estas doenças crónicas exercem um papel importante na morbilidade, influenciando a qualidade de vida relacionada com a saúde, os custos relacionados com a saúde e o prognóstico. Por fim, muitos doentes são mais propensos a morrer das comorbilidades do que pela própria DPOC[8–10]. Como foi recentemente evidenciado por Divo et al., algumas comorbilidades, como a doença coronária, as neoplasias (pulmonar, esofágica, pancreática e mamária), a ansiedade, as arritmias e a fibrose pulmonar intersticial, estão associadas de forma independente ao aumento do risco de morte[11]. Assim, o tratamento da DPOC não deve ser centrado exclusivamente no controlo sintomático e na prevenção das exacerbações, mas deve também ser dirigido às suas manifestações sistémicas e comorbilidades.

A reabilitação respiratória (RR) é uma intervenção não farmacológica que visa restaurar no doente a sua maior capacidade funcional e promover a reintegração social[12,13]. A RR está indicada quando os doentes se mantêm sintomáticos, apesar de terapêutica farmacológica adequada, em todos os graus de gravidade e em todos os escalões etários[1]. A RR deve ser considerada em doentes com dispneia (quando caminham no seu passo habitual ao nível do solo) e com limitações nas suas atividades da vida diária (AVD). A RR pode melhorar os sintomas, a qualidade de vida, a tolerância ao exercício e a participação emocional nas AVD, bem como diminuir a utilização dos recursos de saúde[1,12].

Objetivos

O objetivo deste estudo foi determinar a prevalência das comorbilidades nos doentes com DPOC e avaliar a influência das características basais, assim como das comorbilidades nos resultados da RR.

Métodos

Seleção dos doentes

Neste estudo retrospetivo foram incluídos todos os doentes admitidos num PRR na Unidade de Reabilitação Respiratória nos últimos 5 anos.

O diagnóstico e a classificação espirométrica foram baseados nos critérios do GOLD. Os doentes com insuficiência respiratória crónica (IRC) foram classificados como GOLD IV.

Os processos clínicos foram analisados para a colheita de dados demográficos (idade, sexo e índice de massa corporal), dados clínicos (tabagismo, oxigenoterapia de longa duração [OLD], ventilação não invasiva [VNI]) e exames complementares de diagnóstico (imagiológicos, estudo funcional respiratório, gasometria).

As comorbilidades foram consideradas de acordo com os processos clínicos, que incluíam informação das diferentes especialidades médicas, e foram devidamente confirmadas pela lista medicamentosa e pelos exames complementares de diagnóstico, também disponíveis nos processos clínicos.

Comorbilidades

A comorbilidade é definida como a existência de outra condição médica crónica que existe em associação com a DPOC, não implicando uma relação causal.

Avaliou-se a frequência de cada doença crónica e das doenças associadas:

- cardiovasculares (HTA, insuficiência cardíaca/*cor pulmonale*, doença coronária, arritmia, doença cerebrovascular e doença vascular periférica),
- metabólicas (diabetes mellitus, dislipidémia, excesso de peso/obesidade),
- respiratórias (sequelas de tuberculose pulmonar, bronquiectasias, síndrome de apneia obstrutiva do sono, hipertensão pulmonar, doenças do interstício pulmonar, cancro do pulmão),
- patologia osteoarticular e
- ansiedade/depressão.

Os doentes foram agrupados de acordo com o número de comorbilidades (0, uma e mais do que uma).

Reabilitação respiratória

Todos os doentes foram integrados em PRR após otimização da terapêutica farmacológica e/ou OLD e/ou VNI, e tiveram acesso aos seguintes componentes: educação para a autogestão da doença e para a modificação de fatores de risco, suporte psicossocial e nutricional, técnicas de fisioterapia respiratória e treino de exercício.

O PRR incluiu 8 semanas de treino de exercício, 3 vezes por semana, sob supervisão de um fisioterapeuta. A intensidade alvo do treino era de 80% da potência máxima atingida numa prova de esforço cardiorrespiratória realizada antes do início do PRR. O método de treino aplicado foi o contínuo, com um aumento progressivo do tempo e da intensidade da carga de acordo com o grau de dispneia (4-6 na escala de Borg modificada 0-10) e a monitorização dos sinais vitais, ou o treino intervalado nos doentes com dispneia mais intensa. Cada sessão de treino durava cerca de 30 a 45 min. Os doentes que se encontravam em OLD treinavam com oxigénio suplementar, de forma a manterem a saturação periférica de oxigénio de pelo menos 90%.

A presença de comorbilidades não implicou alterações relevantes do protocolo de treino. No entanto, nos doentes que referiam dispneia intensa durante as sessões de treino de exercício, optava-se por um aumento mais suave do incremento da carga ou pelo treino intervalado, em vez do treino contínuo. Algumas comorbilidades necessitavam de uma monitorização mais cuidadosa, como por exemplo: teste rápido da glicemia capilar em doentes com diabetes mellitus, ou monitorização cardíaca com ECG em doentes com arritmias.

A resposta ao PRR (diferença mínima clinicamente significativa [DMCS]) foi considerada pela melhoria na tolerância ao exercício (+ 30 min na prova de marcha de 6 min [PM6])[14], na dispneia (+ 1 ponto no índice de dispneia de Mahler [IDM]) e na qualidade de vida relacionada com a saúde (− 4 pontos no questionário respiratório de St. George [QRSG])[15,16]. Considerou-se melhoria global quando esta se verificou nos 3 parâmetros referidos.

Estatística

Os dados estão apresentados como média ± desvio padrão para as variáveis contínuas, e como frequência e % para as variáveis categóricas.

A comparação das 2 variáveis foi feita através do teste do X^2 para as variáveis nominais e do teste T de *student* para as variáveis quantitativas.

As variáveis significativas foram posteriormente avaliadas em modelo de regressão logística, considerando a DMCS na melhoria da PM6, do QRSG e do IDM como variáveis dependentes.

Todos os resultados foram considerados estatisticamente significativos para $p \leq 0{,}05$.

A análise estatística foi realizada utilizando o *software* PASW (versão 18; SPSS inc., Chicago, Illinois, Estados Unidos).

Resultados

Este estudo incluiu 114 doentes com DPOC, correspondendo a cerca de 77,6% de todos os doentes admitidos na nossa unidade (fig. 1).

A maioria dos doentes era do sexo masculino (83,3%) e a idade média de 65,8 ± 10,1. Cinco (4,4%), 35 (30,7%), 19 (16,7%) e 55 (48,2%) pertenciam ao estadio I, II, III e IV do GOLD, respetivamente. A média do FEV_1 foi 45,8 ± 16,9% do previsto. A maioria dos doentes (65%) tinha insuficiência respiratória (IR), sendo mais frequente a IR hipoxémica.

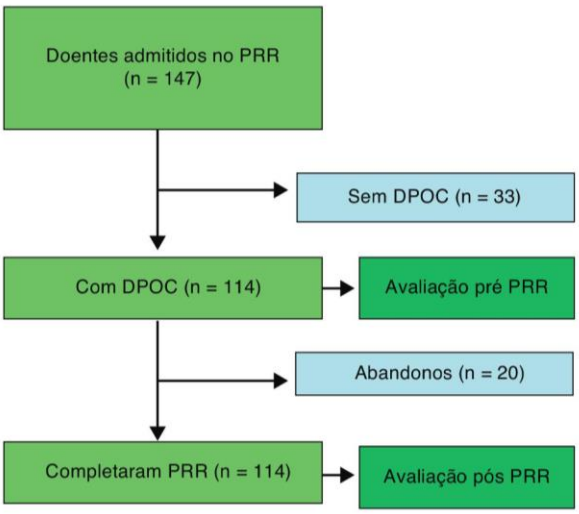


Figura 1 Doentes admitidos no PRR com treino de exercício. DPOC: doença pulmonar obstrutiva crónica; PRR: programa de reabilitação respiratória.

Quarenta e quatro (38,6%) doentes estavam sob OLD e 10 (8,8%) sob VNI (Apêndice, tabela 1).

A distribuição de acordo com o número e o grupo de comorbilidades é apresentado na figura 2. O excesso de peso/obesidade (63,2%) foi a comorbilidade mais prevalente, seguida da HTA (50,9%), das sequelas de tuberculose pulmonar (23,7%), da ansiedade/depressão (21,1%), da insuficiência cardíaca/*cor pulmonale* (20,2%), das bronquiectasias (20,2%), da dislipidémia (19,3%) e da doença coronária (12,3%) (Apêndice, tabela 2).

Entre os 114 doentes com DPOC, 20 não concluíram o PRR. As causas de abandono foram as exacerbações com necessidade de internamento, a doença psiquiátrica e a não adesão ao programa. Não se verificaram diferenças significativas nas características basais e nas comorbilidades entre o grupo de doentes que completou o PRR e o que o abandonou (Apêndice, tabelas 1 e 2).

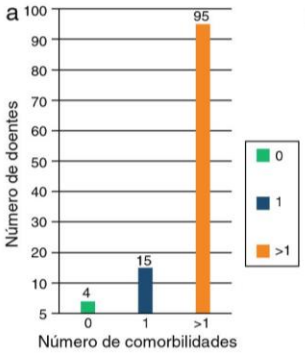
Entre os doentes que concluíram o PRR, 64,9, 64,9 e 51,1% melhoraram para além da DMCS na PM6, no QRSG e no IDM, respetivamente (tabela 1). Apenas 10 (10,6%) doentes não melhoram em nenhum parâmetro e 24 (25,5%) apresentaram melhoria nos 3 parâmetros.

Não se verificou associação estatisticamente significativa entre o número de comorbilidades (0, uma e mais do que uma) e os resultados do PRR (tabela 1). Contudo, houve uma correlação significativa entre algumas características basais e algumas comorbilidades, com a melhoria da qualidade de vida relacionada com a saúde, a dispneia e a tolerância ao exercício.

A IR correlacionou-se inversamente com a melhoria na qualidade de vida relacionada com a saúde ($p = 0,001$; $OR = 0,17$) e com a melhoria global ($p = 0,025$; $OR = 0,33$). Estar sob OLD apresentou uma correlação inversa com a melhoria na dispneia ($p = 0,016$; $OR = 0,313$), a tolerância ao exercício ($p = 0,012$; $OR = 0,32$) e a melhoria global ($p = 0,05$; $OR = 0,337$). Os doentes com pressão arterial de dióxido de carbono baixa ($p = 0,016$) e com pontuação basal no QRSG elevada ($p = 0,06$) apresentaram uma melhoria mais evidente na tolerância ao exercício, e aqueles com menor DLCO melhoraram mais na tolerância ao exercício ($p = 0,032$) e na dispneia ($p = 0,05$) (Apêndice, tabela 3).

Quanto às comorbilidades, a doença coronária correlacionou-se com a melhoria na qualidade de vida relacionada com a saúde ($p = 0,003$; $OR = 0,142$), a ansiedade/

a



b

Comorbilidades	Doentes
Metabólicas	81 (71,1%)
Cardiovasculares	77 (67,5%)
Respiratórias	66 (57,9%)
Ansiedade/Depressão	24 (21,1%)
Osteoarticulares	12 (10,5 %)
Outras	68 (59,6%)

Figura 2 (a) Distribuição de acordo com o número de comorbilidades. (b) Comorbilidades mais frequentes.

Tabela 1 Resultados do PRR e o número de comorbilidades

Melhorias	Total	0 Comorbilidades	1 Comorbilidade	>1 Comorbilidades	p
Tolerância ao exercício	61 (64,9%)	2	6	53	0,113
Qualidade de vida	61 (64,9%)	2	8	51	0,694
Dispneia	48 (51,1%)	2	6	40	0,5
Global	24 (25,5%)	1	1	22	0,171

Tabela 2 Factores preditivos dos resultados do PRR

Variáveis dependentes	Variáveis	B	SE	OR	95% IC		p
					Inferior	Superior	
Melhoria na tolerância ao exercício	OLD	−0,452	0,616	0,636	0,190	2,121	0,463
	Dislipidémia	1,520	0,823	4,573	0,911	22,954	0,065
	FEV_1/FVC	−0,049	0,028	0,952	0,902	1,005	0,073
	DLCO	−0,017	0,016	0,983	0,952	1,014	0,279
Melhoria na qualidade de vida	IR	−1,1588	0,608	0,204	0,062	0,673	0,009
	Doença coronária	−1,632	0,747	0,196	0,045	0,846	0,029
Melhoria na dispneia	OLD	−1,463	0,754	0,232	0,053	1,015	0,52
	Bronquiectasias	1,959	1,126	7,090	0,780	64,477	0,082
	Ansiedade/Depressão	−2,357	0,921	0,095	0,016	0,576	0,011
	$PaCO_2$	0,119	0,067	1,127	0,988	1,285	0,076
	DLCO	−0,016	0,018	0,984	0,949	1,020	0,373
	QRSG	0,03	0,025	1,031	0,982	1,082	0,224
Melhoria global	OLD	−0,580	0,715	0,56	0,138	2,275	0,417
	IR	0,778	0,631	0,459	0,133	1,582	0,218

DLCO: capacidade de difusão do monóxido de carbono; FEV_1: volume expiratório forçado no 1.° segundo; FVC: capacidade vital forçada; IR: insuficiência respiratória; OLD: oxigenoterapia de longa duração; PaCO2: pressão arterial de dióxido de carbono; QRSG: questionário respiratório de St. George.

depressão com a melhoria na dispneia (p = 0,012; OR = 0,247), as bronquiectasias correlacionaram-se positivamente com a melhoria na dispneia (p = 0,04; OR = 3,843), e a dislipidémia com a melhoria na tolerância ao exercício (p = 0,013; OR = 5,86) (Apêndice, tabela 4).

As variáveis significativas foram posteriormente avaliadas em modelo de regressão logística (tabela 2). A IR e a doença coronária influenciaram negativamente a melhoria na qualidade de vida relacionada com a saúde. A ansiedade/depressão relacionou-se com uma melhoria menos acentuada na dispneia.

Discussão

Este estudo confirma que as comorbilidades são prevalentes nos doentes com DPOC referenciados aos PRR. Outros autores, como Mapel et al., descreveram uma média de 3,7 comorbilidades em doentes com DPOC, comparado com 1,8 em indivíduos saudáveis[17].

As comorbilidades mais frequentemente associadas à DPOC foram as cardiovasculares, as outras patologias respiratórias e a ansiedade/depressão, em linha com o descrito na literatura[5,11]. A seguir ao excesso de peso/obesidade, a HTA foi a segunda comorbilidade mais prevalente no nosso grupo de doentes, enquanto, no trabalho de Divo et al., foi a mais frequente. Por outro lado, um número significativo dos nossos doentes apresentava comorbilidades que foram associadas a um maior risco de mortalidade por estes autores, como a insuficiência cardíaca, a doença coronária e a ansiedade[11].

A associação com a doença cardiovascular é já conhecida[18]. O FEV_1 é um fator preditivo de morte por enfarte do miocárdio. A rigidez arterial sistémica é um fator preditivo importante de doença vascular[19] e está aumentada na DPOC. A presença de inflamação sistémica estimula a aterosclerose coronária, resultando em isquémia. Assim, a DPOC é um fator de risco independente para a doença coronária[18].

Cerca de 40 a 50% dos indivíduos dos países industrializados com 60 ou mais anos de idade apresentam critérios diagnósticos de síndrome metabólica[20]. Esta síndrome representa um conjunto de fatores de risco (obesidade abdominal, dislipidémia aterogénica, HTA e resistência à insulina) que predispõem os doentes à inflamação sistémica, à doença cardiovascular e à inatividade física, e frequentemente coexistem com a DPOC[20–22].

Outras patologias respiratórias foram identificadas nos nossos doentes. A elevada frequência de sequelas de tuberculose pulmonar e de bronquiectasias reflete o facto de a tuberculose pulmonar ainda ser comum em Portugal, apesar de ter diminuído nas últimas décadas[23,24]. Por outro lado, a prevalência da síndrome de apneia obstrutiva do sono deve-se, provavelmente, ao facto de grande parte da população estudada ter excesso de peso.

A ansiedade/depressão é uma comorbilidade altamente prevalente na DPOC. Hill et al. também verificaram que mais de 42% dos doentes com DPOC apresentavam sintomas de ansiedade/depressão[25]. Sabe-se que a ansiedade/depressão está relacionada com o grau de dispneia e com a sensação de incapacidade nos doentes com DPOC. A dispneia é o sintoma mais perturbador e, como forma de o evitar, o doente diminui a sua atividade física. O sedentarismo condiciona um menor envolvimento emocional e físico nas atividades da vida diária, o isolamento social e o agravamento da qualidade de vida relacionada com a saúde. A ansiedade/depressão associa-se a maior morbilidade da DPOC, pior qualidade de vida, com mais dispneia e com maior utilização dos recursos de saúde e, até mesmo, maior mortalidade[26]. Estudos anteriores relatam um impacto negativo da ansiedade/depressão na PM6 e na qualidade de vida[27,28]. Da mesma forma, demonstramos que doentes ansiosos/deprimidos integrados em PRR apresentam uma melhoria menos acentuada na dispneia.

Os doentes com doença coronária referem um menor ganho na qualidade de vida relacionada com a saúde com o PRR. Crisafulli et al. demonstraram que a patologia cardíaca apresenta uma relação inversa com a melhoria na qualidade de vida relacionada com a saúde[29]. A dispneia, a fadiga e a diminuição da força muscular podem justificar a menor qualidade de vida nesses doentes. Vanfleteren et al. descreveram que as alterações isquémicas no ECG são comuns nos doentes com DPOC e estão associadas a piores resultados nos PRR[30]. No entanto, a reabilitação tem benefícios bem conhecidos nos doentes com doença coronária e insuficiência cardíaca, como a melhoria na capacidade funcional, no prognóstico e no bem-estar[31].

A prevalência de, pelo menos, uma comorbilidade foi maior (96,5%) no nosso grupo do que o relatado em outros estudos (65%, Crisafulli 2008[29]), mas semelhante ao documentado por Mapel (apenas 6% dos doentes com DPOC não tinham outra patologia associada[17]). A elevada prevalência de comorbilidades na nossa população pode ser explicada pelo facto de a maioria dos doentes ter um historial de tabagismo, uma idade média superior a 60 anos e um predomínio do grau IV de DPOC, todos fatores que contribuem para uma inflamação sistémica mais pronunciada. A inflamação sistémica é um mecanismo potencialmente comum às consequências sistémicas da DPOC e às suas comorbilidades[5,32–35].

Os resultados do PRR foram semelhantes em todos os grupos de comorbilidades (0, uma e mais do que uma), contrariamente ao relatado por Crisafulli[29], que descreveu benefícios na dispneia e na qualidade de vida mais notórios nos doentes com menos comorbilidades. Contudo, deve-se salientar que o presente estudo tem uma limitação quanto ao número de doentes sem comorbilidades. Este grupo é muito pequeno, havendo uma diferença significativa entre os subgrupos de comorbilidades (4 doentes – 0 comorbilidades, 15 doentes – uma comorbilidade, 95 doentes – mais do que uma comorbilidade), o que não permite concluir sobre o impacto concreto do número das comorbilidades nos resultados do PRR na população estudada. Esta limitação poderá ser ultrapassada com uma maior amostra de doentes.

Quase metade (48,2%) dos nossos doentes pertencia ao GOLD IV e apenas 16,7% ao GOLD III. Apesar de esta não ser a distribuição usual dos graus de gravidade nos PRR na maioria dos centros, esta diferença pode ser explicada pelo facto de a nossa unidade de RR também admitir doentes após exacerbações com IR (65%). Os autores incluíram os doentes com IRC no GOLD IV, tal como seriam classificados nos critérios do GOLD anteriores a 2011. Embora o nosso grupo apresente um predomínio de doentes em estadio IV do GOLD, não existiram diferenças estatisticamente significativas nos resultados relativos aos vários graus espirométricos, refletindo os benefícios da RR em todos os graus de gravidade.

Assinalamos que a população estudada é composta por 83% de doentes do sexo masculino e que esta não é a distribuição típica por géneros nos PRR. No entanto, a DPOC em Portugal é mais prevalente nos homens (18,7 versus 10,5%)[36]. Neste estudo, as comorbilidades (tanto em número como em tipo) não diferiram entre os doentes do sexo masculino e os do sexo feminino (dados não apresentados).

Algumas das características basais correlacionaram-se com os resultados. Os doentes com IR apresentaram um menor ganho na qualidade de vida relacionada com a saúde. A hipoxémia pode condicionar um limiar anaeróbio diminuído durante o exercício, o que determina um aumento precoce da frequência respiratória, com consequente aumento na hiperinsuflação dinâmica, um maior grau de dispneia e uma maior limitação nas AVD, o que, por sua vez, promove o descondicionamento e o sedentarismo[37,38].

Apesar das correlações descritas, os doentes com DPOC e outras doenças crónicas não são maus candidatos à RR e tal não significa necessariamente que irão ter menor benefício. Todos os doentes podem beneficiar da RR, que é uma abordagem terapêutica holística para a DPOC, e os benefícios do treino de exercício nas várias comorbilidades estão bem documentados[39].

Conclusões

Nos doentes com DPOC, as comorbilidades são fatores determinantes na qualidade de vida relacionada com a saúde e no prognóstico.

O nosso estudo confirma que a maioria dos doentes referenciados a um PRR apresenta uma ou mais comorbilidades, incluindo metabólicas, cardiovasculares, respiratórias, ansiedade/depressão e patologia osteoarticular.

A abordagem de doentes com DPOC deve incluir a identificação ativa das comorbilidades associadas, de forma a otimizar a estratégia terapêutica. A RR é uma abordagem holística direcionada não só para o controlo dos sintomas respiratórios, mas também para os efeitos sistémicos.

Apesar de algumas patologias como a IR e a doença coronária poderem diminuir o impacto dos benefícios da reabilitação, este estudo salienta que as comorbilidades, tanto isoladas como em combinação, se clinicamente controladas, não impedem o acesso à reabilitação.

Responsabilidades éticas

Proteção de pessoas e animais. Os autores declaram que para esta investigação não se realizaram experiências em seres humanos e/ou animais.

Confidencialidade dos dados. Os autores declaram ter seguido os protocolos de seu centro de trabalho acerca da publicação dos dados de pacientes e que todos os pacientes incluídos no estudo receberam informações suficientes e deram o seu consentimento informado por escrito para participar nesse estudo.

Direito à privacidade e consentimento escrito. Os autores declaram ter recebido consentimento escrito dos pacientes e/ou sujeitos mencionados no artigo. O autor para correspondência deve estar na posse deste documento.

Autoria

Alexandra Carreiro colheu e analisou os dados (incluindo a análise estatística) e elaborou o projeto do artigo. Joana Santos colheu e analisou os dados e colaborou na elaboração

do artigo. Fátima Rodrigues concebeu o estudo, fez colheita dos dados, realizou a sua análise e supervisionou todos os aspetos do estudo.

Conflito de interesses

Os autores declaram não haver conflito de interesses.

Apêndice. Material adicional

Pode consultar o material adicional para este artigo na sua versão eletrónica disponível em doi:10.1016/j.rppneu.2012.12.004.

Bibliografia

1. Rodriguez-Roisin R, Anzueto A, Bourbeau J, S. de Guia T, Hui D, Martinez F, et al. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategies for diagnosis, management and prevention of COPD (Update 2011). Global Initiative for Obstructive Lung Disease, Inc. 2011.
2. Horton R. The neglected epidemic of chronic disease. Lancet. 2005;366:1514.
3. OMS, World Health Statistics 2008, http://www.who.int/gard/news_events/World_Health_Statistics_2008/en/ [consultado 13 Fev 2012].
4. Nussbaumer-Ochner Y, Rabe KF. Systemic manifestations of COPD. Chest. 2011;139:165–73.
5. Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ. Comorbidities in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008;5:549–55.
6. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009;33:1165–85.
7. Raherison C, Girodet PO. Epidemiology of COPD. Eur Respir Rev. 2009;18:213–21.
8. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. Ascertainment of cause-specific mortality in COPD: Operations of the TORCH Clinical Endpoint Committee. Thorax. 2007;62:411–5.
9. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: A randomized clinical trial. Ann Intern Med. 2005;142:233–9.
10. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: Role of comorbidities. Eur Respir J. 2006;28:1245–57.
11. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186:155–61.
12. Nici L, Dommer C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med. 2006;173:1390–413.
13. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest. 2007;131:4S–2S.
14. Puhan MA, Chandra D, Mosenifar Z, Ries A, Mke B, Hansel NN, et al. The minimal important difference of exercise tests in severe COPD. Eur Resp J. 2011;37:784–90.
15. Jones PW. Health status measurement in chronic obstructive pulmonary disease. Thorax. 2001;56:880–7.
16. De Torres JP, Pinto-Plata V, Ingenito E, Bagley P, Gray A, Berger R, et al. Power of outcome measurements to detect clinically significant changes in pulmonary rehabilitation of patients with COPD. Chest. 2002;121:1092–8.
17. Mapel DW, Hurley JS, Frost FJ, Peterson HV, Picchi MA, Coultas DB. Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. Arch Intern Med. 2000;160:2653–8.
18. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. Proc Am Thorac Soc. 2005;2:8–11.
19. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner R, Connett J. The effects of a smoking cessation intervention on 14.5-year mortality: A randomized clinical trial. Ann Intern Med. 2005;142:233–9.
20. Watz H, Waschki B, Kirsten A, Müller KC, Kretschmar G, Meyer T, et al. The metabolic syndrome in patients with chronic bronchitis and COPD: Frequency and associated consequences for systemic inflammation and physical inactivity. Chest. 2009;136:1039–46.
21. Poulain M, Doucet M, Drapeau V, Fournier G, Tremblay A, Poirier P, et al. Metabolic and inflammatory profile in obese patients with chronic obstructive pulmonary disease. Chron Respir Dis. 2008;5:35–41.
22. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735–52.
23. Lee JH, Chang JH. Lung function in patients with chronic airflow obstruction due to tuberculous destroyed lung. Respir Med. 2003;97:1237–42.
24. Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. Thorax. 2000;55:32–8.
25. Hill K, Geist R, Goldstein RS, Lacasse Y. Anxiety and depression in end-stage COPD. Eur Respir J. 2008;31:667–77.
26. Von Leupoldt A, Taube K, Lehmann K, Fritzsche A, Magnussen H. The impact of anxiety and depression on outcomes of pulmonary rehabilitation in patients with COPD. Chest. 2011;140:730–6.
27. Cully JA, Graham DP, Stanley MA, Fergusson CJ, Sharafkhaneh A, Souchek J, et al. Quality of life in patients with chronic pulmonary disease and comorbid anxiety or depression. Psychosomatics. 2006;47:312–9.
28. Giardino ND, Curtis JL, Andreia AC, Fans VS, Benditt JO, Lyubknin M, et al. Anxiety is associated with diminished exercise performance and quality of life in severe emphysema: A cross-sectional study. Respir Res. 2010;11:29.
29. Crisafulli E, Costi S, Luppi F, Cirelli G, Cilione C, Coletti O, et al. Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. Thorax. 2008;63:487–92.
30. Vanfleteren L, Franssen FM, Uszko-Lencer NH, Spruit MA, Celis M, Gorgels AP, et al. Frequency and relevance of ischemic electrocardiographic findings in patients with chronic obstructive pulmonary disease. Am J Cardiol. 2011;108:1669–74.
31. Piepoli MF, Corrà U, Benzer W, Bjarnason-Wehrens B, Dendala P, Gaita D, et al. Secondary prevention through cardiac rehabilitation: From knowledge to implementation. A position paper from Cardiac Rehabilitation section of the European Association of Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil. 2010;17:1–17.
32. Sevenoaks MJ, Stockley RA. Chronic Obstructive Pulmonary Disease, inflammation and comorbidities – a common inflammatory phenotype? Respir Res. 2006;7:70.
33. Fabbri LM, Luppi F, Beghé B, Rabe KF. Complex chronic comorbidities of COPD. Eur Respir J. 2008;31:204–12.
34. Rabinovich RA, MacNee W. Chronic obstructive pulmonary disease and its comorbidities. Br J Hosp Med (Lond). 2011;72:137–45.
35. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet. 2007;370:797–9.

36. Barbara C, Rodrigues F, Dias H, Cardoso J, Almeida J, Matos MJ, et al. COPD prevalence in Lisbon, Portugal: The burden of obstructive lung disease study (BOLD). Rev Port Pneumol. In press 2013. http://dx.doi.org/10.1016/j.rppneu.2012.11.004.
37. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;171:972–7.
38. Vagaggini B, Costa F, Antonelli S, Se Simone C, De Cusatis G, Martino F, et al. Clinical predictors of the efficacy of a pulmonary rehabilitation programme in patients with COPD. Respir Med. 2009;103:1224–30.
39. Crisafulli E, Gorgone P, Vagaggini B, Pagani M, Rossi G, Costa F, et al. Efficacy of standard rehabilitation in COPD outpatients with comorbidities. Eur Respir J. 2010;36:1042–8.

Pulmonary Rehabilitation in COPD: Effect of 2 Aerobic Exercise Intensities on Subject-Centered Outcomes—A Randomized Controlled Trial

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BACKGROUND: Exercise training is an important component of pulmonary rehabilitation, but it remains questionable how training intensity affects patient-centered outcomes. The aim of this study was to compare the effects of 2 aerobic training intensities on health-related quality of life (HRQOL), symptom control, and exercise tolerance in subjects with COPD. METHODS: Thirty-four subjects with mild to very severe COPD participated in an equivalence/non-inferiority randomized controlled trial with a parallel group blinded to 60 or 80% maximum work rate (W_{max}) aerobic training intensity. The intervention was an out-patient pulmonary rehabilitation program conducted 3 times/week for 8 weeks. Outcomes were assessed with the St George Respiratory Questionnaire (primary outcome), Mahler's dyspnea index, London Chest Activity of Daily Living scale, 6-min walk test, and constant-load and incremental exercise tests. RESULTS: Subjects were randomly allocated to aerobic training intensity of 60% W_{max} (group 1, $n = 17$) or 80% W_{max} (group 2, $n = 17$). Although there were significant improvements in all outcomes for both groups, there were no between-group differences in mean change in the St George Respiratory Questionnaire ($P = .31$, 95% CI −12.0 to 3.9), Mahler's dyspnea index ($P = .38$), London Chest Activity of Daily Living scale ($P = .92$), 6-min walk test ($P = .50$, 95% CI 6.2–71.1), constant-load exercise test ($P = .50$), and incremental exercise test ($P = .12$). There was only one exercise-related adverse event of cardiac symptoms. CONCLUSIONS: Aerobic training intensity of at least 60% W_{max} has a positive impact on COPD patient-centered outcomes, with no additional benefit of increasing intensity to 80% W_{max} in HRQOL, symptom control, and exercise tolerance, challenging the present clinical attitude of rehabilitation professionals. (ClinicalTrials.gov registration NCT01944072.) *Key words: COPD; rehabilitation; exercise intensity; aerobic training; health-related quality of life.* [Respir Care 2015;60(11):1603–1609. © 2015 Daedalus Enterprises]

Introduction

COPD is the world's fourth leading cause of mortality[1] and is projected in 2020 to be the fifth leading disease in morbidity impact.[2] Exercise intolerance in these patients is multifactorial and explained by several known mechanisms.[3–5] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends, with level A evidence, pulmonary rehabilitation programs to all symptom-

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The authors have disclosed no conflicts of interest.

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atic patients with COPD.[6] Although this exercise-based treatment is scientifically established in published guidelines,[7–12] there is a wide range of studies presenting diverse exercise-training methodologies in clinical practice.[13,14] Aerobic exercise training is recommended 3–5 times/week for at least 20 sessions of 30–90 min at 60–80% maximum work rate (W_{max}) of continuous or intermittent use of a treadmill, bicycle, step, elliptic, or rowing machine.[7,15,16] Current investigation has not yet identified the critical exercise intensity,[17] but it is established that physiological benefits are achieved with a minimum of 60% W_{max} and that the higher the intensities, the greater the physiological benefits.[10,13,18] Furthermore, it has not been proven conclusively that these physiological benefits would lead to greater improvements in patient-centered outcomes.[7,15,16] Current patient-centered outcomes provide the strongest evidence of the impact of pulmonary rehabilitation programs on patients with COPD[19] by measuring improvement in symptoms, exercise performance, and quality of life, which are the most meaningful changes for the patient. Considering the intensity range recommended by international guidelines of 60–80% W_{max}, we do not know whether higher intensities achieve the best impact on patient-centered outcomes. For this purpose, we tested the hypothesis that 2 aerobic training intensities (60 and 80% W_{max}) had equal or non-inferior effects on COPD patient-centered outcomes: health-related quality of life (HRQOL), symptom control, and exercise tolerance.

QUICK LOOK

Current knowledge

COPD is the world's fourth leading cause of mortality and is projected to be the fifth leading disease in morbidity impact by 2020. Exercise intolerance in these patients is associated with both worsening morbidity and mortality. Pulmonary rehabilitation including exercise training has met with mixed results in improving quality of life and symptoms. The optimum intensity of exercise during rehabilitation is frequently debated.

What this paper contributes to our knowledge

During pulmonary rehabilitation, aerobic training intensity of at least 60% maximum work rate (W_{max}) had a positive impact in COPD subject-centered outcomes, with no additional benefit of increasing intensity to 80% W_{max} in health-related quality of life, symptom control, and exercise tolerance. Work intensity needs to be sufficient to provide benefit without resulting in exercise intolerance.

Methods

This was an equivalence/non-inferiority trial with blocked stratified randomization of subject-blinded assignment in a parallel group design, with an allocation ratio of 1:1. Eligible participants were stable subjects with COPD, with $FEV_1/FVC < 0.70$, recruited by medical referral for exercise training. Exclusion criteria were inability to attend a program 3 times/week; metastatic neoplasia; infectious or unstable cardiac diseases; and neuromusculoskeletal, psychiatric, or cognitive disorders. The trial was conducted between January 2009 and March 2010 at the Hospital Pulido Valente in Lisbon, Portugal, with an experienced pulmonary rehabilitation program, which serves 350,000 inhabitants. The hospital's ethics committee and administrative board approved the trial conduction (institutional review board DIRCLIN-07.ABR.2009-0256), and all subjects gave written informed consent. The trial is registered as NCT01944072.

The intervention consisted of a 20-session out-patient pulmonary rehabilitation program of therapeutic exercise (aerobic, strength, and flexibility) plus education and skills training. Aerobic exercise was 30 min of training 3 times/week on a treadmill (Light Commercial Europe, Mercury BH, Vitoria-Gasteiz, Spain) or bicycle (Erg602BE, Dimeq, Berlin, Germany) according to subjects' preference, with an intensity of 60% W_{max} (group 1) or 80% W_{max} (group 2) of an initial incremental exercise test.[3] Strength training was combined 2 times/week with multi-station equipment (CybexMG500 Multi-Gym, Cybex, Medway, MA) in 3 sets of 8 repetitions at 50% of one-repetition maximum for selected exercises (seated leg press, seated calf raise, seated row, abdominal crunch, and chest press). Flexibility training was combined 3 times/week with 5 s of stretching for each of 7 selected large body muscle exercises. There were 5 education and skills training group-oriented sessions: COPD, medication and respiratory devices, breathing exercises, bronchial hygiene techniques, and benefits of physical exercise. HRQOL was the primary outcome measured by the St George Respiratory Questionnaire (SGRQ),[20] with a score ranging from 0 to 100, with higher scores meaning worse HRQOL. Secondary outcomes were symptom control measured by Mahler's dyspnea index[21] (scores ranging from −9 to +9, with positive scores meaning improvement in dyspnea) and by the London Chest Activity of Daily Living (LCADL) scale[22] (scores ranging from 0 to 75, with higher scores meaning more limitations on activities of daily living) and exercise tolerance assessed by a 6-min walk test (6MWT)[23] (functional capacity), incremental exercise test[3] (peak aerobic capacity), and constant-load exercise test[3] (endurance capacity). The minimum clinically important differences were: ±4 for the SGRQ,[24,25] 1 point for the transitional dyspnea index,[24–26] 25 m for the 6-min walk distance (6MWD),[27]

and 100 s for the constant-load exercise test.[28,29] The incremental exercise and constant-load exercise tests were assessed before and after the pulmonary rehabilitation program; all other outcomes were also accessed at the tenth session for intention-to-treat analysis. Considering the primary outcome, 34 subjects were studied for a clinically important target difference of 12 points in the SGRQ[24,25] between intervention groups (group 1, $n = 17$; group 2, $n = 17$). This sample size was statistically calculated using the PS: Power and Sample Size Calculation program (Vanderbilt University, Nashville, Tennessee), with 5% significance level, a power of 80%, an SGRQ SD of 11.33 points,[30] and a 10% predicted dropout rate. A subject's allocation sequence was computer-generated, and the randomization was stratified by a cutoff value of 0.50 FEV_1, with an allocation ratio of 1:1 using random block sizes of 2 (mild to moderate COPD, severe to very severe COPD). The research physiotherapist assessed eligibility, discussed the trial, and obtained informed consent from the subject. Another physiotherapist adapted the subject to the treadmill or bicycle, and only after the chest physician assessed the subject by an incremental exercise test was an allocation consignment given according to a schedule maintained in a safe deposit box. This was a subject-blinded study, as all subjects participated in the same pulmonary rehabilitation program with individualized aerobic intensity training from the incremental exercise test but could not differentiate who was training at 60 or 80% W_{max}. Blinding was not applied to health-care providers due to their role in monitoring intensity targets of aerobic training. Statistical analysis was conducted with PASW Statistics 18.0.0 (SPSS, Chicago, Illinois), with a modified intention-to-treat analysis considering a minimum of 10 sessions of attendance of the pulmonary rehabilitation program. Primary outcome was change in the SGRQ, with the total and impact scores analyzed with the Satterthwaite test (normal distribution and unequal variances) and activity and symptom scores analyzed with the Student *t* test (normal distribution and equal variances). Secondary outcomes were change in the transitional dyspnea index, LCADL scale, incremental exercise test, and constant-load exercise test (analyzed by the Mann-Whitney *U* test, non-normal distribution) and change in 6MWD (analyzed by the Student *t* test, normal distribution and equal variances). All outcomes were also analyzed for inferential statistics with the Pearson coefficient (continuous variable) except for the transitional dyspnea index and LCADL scale, which were analyzed with the Spearman coefficient (ordinal variable).

Results

As shown in Figure 1, a total of 56 subjects were recruited between January and December of 2009, with 22 excluded, and the trial was stopped when the sample size goal was achieved ($n = 34$). The intervention phase was February 2009 to March 2010. Table 1 presents subjects' baseline demographic and clinical characteristics. The 20-session pulmonary rehabilitation program had a mean duration of 8.2 ± 1.8 weeks for group 1 and 7.9 ± 2.9 weeks for group 2.

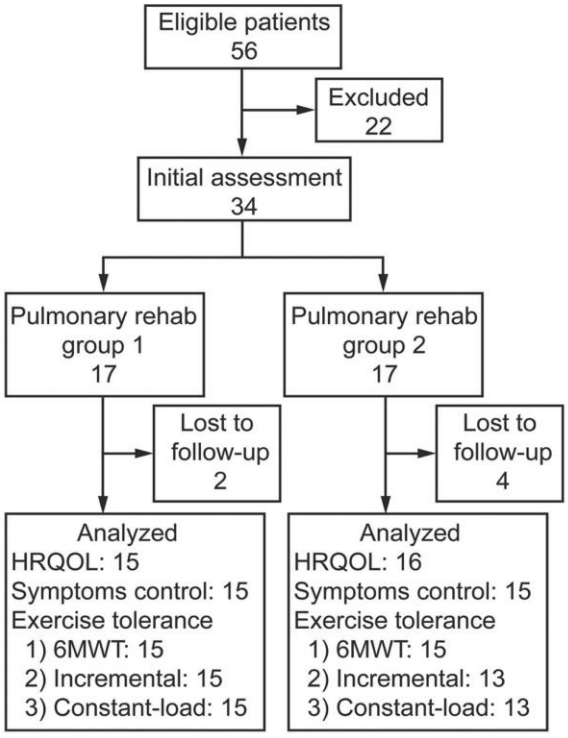

Fig. 1. Flow chart. HRQOL = health-related quality of life. 6MWT = 6-min walk test.

For the purpose of analysis, treadmill and bicycle intensity units were converted to metabolic equivalents by American College of Sports Medicine formulas.[31] The mean intensity of the aerobic exercise training was 4.3 ± 0.9 metabolic equivalents for group 1 and 5.5 ± 1.8 metabolic equivalents for group 2, which correspond to an overall mean efficiency of aerobic training intensity exercised/prescribed of 87.1% (group 1 = 92%, group 2 = 82%). Determined by the subjects' choice, both groups were similar, considering the training modality (76% treadmill and 24% bicycle) and the type of training (94% continuous and 6% interval). All subjects had 100% efficiency of strength training intensity exercised/prescribed (ie, 50% of one-repetition maximum) and attended the education and skills training group sessions as programmed.

The primary analysis was modified intention to treat with 31 of 34 subjects randomly assigned (see Fig. 1) due

Table 1. Demographic and Clinical Baseline Data

	Group 1: 60% W_{max} (n = 17)	Group 2: 80% W_{max} (n = 17)
Sex, *n* (%)		
Male	12 (70.6)	15 (88.2)
Female	5 (29.4)	2 (11.8)
Age, mean ± SD y	66.9 ± 11.4	67.3 ± 10.4
Education level, *n* (%)		
Elementary school	5 (29.4)	4 (23.5)
Secondary education	9 (52.9)	10 (58.8)
Higher education	3 (17.6)	3 (17.6)
Professional activity, *n* (%)		
Unemployed	1 (5.9)	1 (5.9)
Active	3 (17.6)	1 (5.9)
Retired	13 (76.5)	15 (88.2)
Pulmonary function, mean ± SD		
FVC, L	3.0 ± 1.0	3.5 ± 0.9
FVC, % predicted	87.8 ± 20.3	96.4 ± 19.3
FEV_1, L	1.4 ± 0.4	1.6 ± 0.5
FEV_1, % predicted	54.1 ± 15.6	55.7 ± 16.4
FEV_1/FVC	0.48 ± 0.12	0.45 ± 0.10
Oxygen therapy, *n* (%)	0 (0.0)	2 (11.8)
Risk factors, *n* (%)		
Hypertension	10 (58.8)	10 (58.8)
Dyslipidemia	3 (17.6)	2 (11.8)
Diabetes mellitus	2 (11.8)	0 (0.0)
Alcoholism	2 (11.8)	0 (0.0)
Ex-drug user	1 (5.9)	1 (5.9)
Obesity	1 (5.9)	0 (0.0)
Comorbidities, *n* (%)		
Pulmonary tuberculosis (sequelae)	4 (23.5)	2 (11.8)
Obstructive sleep apnea syndrome	3 (17.6)	1 (5.9)
Rhinitis/sinusitis	3 (17.6)	1 (5.9)
Ischemic heart disease	3 (17.6)	1 (5.9)
Benign prostatic hyperplasia	1 (5.9)	3 (17.6)
Hypoxemic respiratory failure	2 (11.8)	1 (5.9)
Bronchiectasis	1 (5.9)	1 (5.9)
Gastroesophageal reflux	1 (5.9)	1 (5.9)
Osteoporosis	1 (5.9)	0 (0.0)

W_{max} = maximum work rate

to follow-up loss of 3 subjects before the tenth session of the pulmonary rehabilitation program (respiratory infection, professional reasons, and lower-limb pain). Secondary analysis of Mahler's dyspnea index, LCADL scale, and 6MWT was carried out on 30 subjects because of the loss to follow-up of one subject (thyroid dysfunction with atrial fibrillation) at the thirteenth session of the pulmonary rehabilitation program without completing the overall assessment; the constant-load exercise and incremental exercise tests were analyzed for 28 subjects since there were a total of 6 subjects lost to follow-up (the above-mentioned 4 and another 2 due to an elective intestinal surgery and a lack of motivation).

As shown in Table 2, there was significant improvement in all outcomes, as all results exceeded the known minimum clinically important difference in both groups. Each group exceeded a 3-fold minimum clinically important difference of 1 point in the transitional dyspnea index[24–26] (almost a 4-fold minimum clinically important difference of 25 m in the 6MWD)[27] and improved by > 100 s the minimum clinically important difference in the constant-load exercise test,[28,29] and both groups presented an improvement in the LCADL scale and incremental exercise test but without any clinical conclusion regarding its unknown minimum clinically important difference.

In primary analysis, the difference in mean changes in HRQOL between groups was not statistically significant. Although each group differed by > 4 points in the minimum clinically important difference[24,25] in all SGRQ scores, between groups, the results fell short of the 12-point effect size predefined in the trial design. In secondary analysis, the difference between groups in mean changes as an effect of aerobic training intensity of 60 or 80% W_{max} in HRQOL, symptom control, and exercise tolerance was also not statistically significant.

As expected by the ancillary analysis, age was inversely correlated with the 6MWD (initial 6MWD, $\rho = -0.45$, $P = .01$; final 6MWD, $\rho = -0.53$, $P < .001$) and with duration of the constant-load exercise test (initial constant-load exercise test, $\rho = -0.48$, $P = .01$; final constant-load exercise test, $\rho = -0.62$, $P < .001$). Nevertheless, there was no statistical correlation between age and improvements in the 6MWD ($\rho = 0.07$, $P = .71$) and constant-load exercise test ($\rho = -0.27$, $P = .16$).

There were 5 adverse events during the trial, only one exercise-related, during the eleventh session of the pulmonary rehabilitation program with tachycardia, arrhythmia, and angina in a subject with heart disease history (group 1). After acute heart ischemia was excluded in the emergency room, the subject returned to the pulmonary rehabilitation program, which concluded without any other adverse events. Other adverse events not exercise-related were lower-limb pain related to lumbar hernia in one subject (group 2); gastrointestinal symptoms in 2 subjects (group 2), with one being surgically treated; thyroid dysfunction with atrial fibrillation in one subject (group 2); and respiratory infection in another one (group 1).

Discussion

In the literature, aerobic training protocols present a wide variety of types, modalities, durations, frequencies, and intensities, making a rigorous comparison of published findings difficult. This study outlined the equivalence effect of 2 aerobic training intensities on patient-centered outcomes. The main conclusion is that there were significant improvements in all outcomes for both intensities (60

Table 2. Results

Outcome	Group 1: 60% W_{max} (n = 17)	Group 2: 80% W_{max} (n = 17)	Effect size	
			P	95% CI
HRQOL				
Change in SGRQ, %				
Total	−14.7 ± 13.0	−10.6 ± 7.4	.31	−12.0 to 3.9
Symptoms	−15.7 ± 19.2	−13.5 ± 15.0	.72	−14.8 to 10.4
Activity	−17.4 ± 14.6	−11.0 ± 13.7	.21	−16.8 to 4.0
Impact	−12.7 ± 16.2	−9.5 ± 7.9	.50	−12.8 to 6.5
Symptom control				
Change in Mahler's dyspnea index, points	3.0 ± 2.8	3.5 ± 3.5	.38	
Change in LCADL scale, points	−2.3 ± 2.5	−1.5 ± 3.5	.42	
Exercise tolerance				
Change in 6MWD, m	98.9 ± 109.0	95.4 ± 67.0	.92	−64.2 to 71.1
Change in incremental exercise test, metabolic equivalents	1.3 ± 1.1	1.7 ± 0.9	.12	
Change in constant-load exercise test, s	135.7 ± 433.8	118.0 ± 151.1	.50	

Data are mean ± SD.
W_{max} = maximum work rate
HRQOL = health-related quality of life
SGRQ = St George Respiratory Questionnaire
LCADL = London Chest Activity of Daily Living
6MWD = 6-min walk distance

and 80% W_{max}), but there were no differences between groups in mean changes in HRQOL, symptom control, and exercise tolerance.

Effect of Aerobic Training Intensity on HRQOL

The methodology of the pulmonary rehabilitation program with the SGRQ as an outcome is hugely diverse in the published studies, as shown by the meta-analysis of Lacasse et al[32] and the systematic review of Puhan et al.[33] These publications did not address the isolated effect of aerobic training intensity on patient-centered outcomes, and the evidence presented favoring high versus low intensity was weak. There is evidence of a positive effect on HRQOL, as shown by studies by Bernard et al,[34] Pereira et al,[35] Montes de Oca et al,[36] Dourado et al,[37] Arnardóttir et al,[38] and Foglio et al,[39], even considering the wide range of intensities in those heterogeneous pulmonary rehabilitation program interventions (type, modality, duration, and frequency). The multi-center study by Laviolette et al[28] with 168 subjects with COPD also found improvement in the SGRQ after the pulmonary rehabilitation program but lacked any description of the exercise intensity applied. As far as we know, only the Normandin study[40] with 40 subjects with COPD in an 8-week pulmonary rehabilitation program compared high (at least 80% W_{max}) with moderate intensity (calisthenics class). They found no differences between groups in HRQOL assessed by the chronic respiratory questionnaire. Our study also outlines the equivalence impact of moderate and high aerobic intensities on HRQOL but further refines moderate intensity as 60% W_{max} and high intensity as 80% W_{max} in a comparable exercise prescription.

Effect of Aerobic Training Intensity on Symptom Control

The results of this study show that aerobic intensity of at least 60% W_{max} has a positive impact on symptom control assessed by the transitional dyspnea index, without any superior effect of higher intensities. These findings are in accordance with the above-mentioned studies by Dourado et al,[37] Foglio et al,[39] and Normandin et al[40] with no differences between groups.

Effect of Aerobic Training Intensity on Exercise Tolerance

International guidelines present evidence of physiological benefits associated with higher aerobic training intensities,[41] in accordance with historical studies by Casaburi et al,[42] Maltais et al,[43] Puente-Maestu et al,[44] and Gimenez et al,[45] but also more recently by Lacasse et al,[32] Laviolette et al,[28] Bernard et al,[34] Montes de Oca et al,[36] Dourado et al,[37] Arnardóttir et al,[38] Foglio et al,[39] Normandin et al,[40] and Hsieh et al.[46] Those studies reported improvements in the 6MWT, incremental exercise test, and constant-load exercise test with a pulmonary rehabilitation program but without any evidence of significant differences in these outcomes as an effect of the aerobic

training intensities applied. On the other hand, more research is needed focusing on patients' goals.[47] The results of our study demonstrate that there is no superior effect of higher intensities in aerobic training on patient-centered outcomes. Therefore, different physiological effects as a result of different training intensities might have a similar impact on patients with COPD.

Overall, there were no differences between groups in mean changes in HRQOL, symptom control, and exercise tolerance as a result of aerobic training at 60 or 80% W_{max}. Perhaps the impact on patient-centered outcomes would be best achieved by designing specific training activities related to the patient's real living environment, regardless of the intensity of $\geq 60\%$ W_{max}.

Age Correlation With the 6MWT and Constant-Load Exercise Test

According to our study, the older subjects walked shorter distances in the 6MWT and achieved shorter durations in the constant-load exercise test, both at baseline and during final assessments, but interestingly, there was no relation between age and improvement in these exercise-related outcomes. This indicates that age cannot be a predictive factor for the level of benefit from a pulmonary rehabilitation program, and this fact must be taken into account when enrolling elderly subjects.

Limitations

Among the 34 subjects studied, there were 6 adverse events, only one of them exercise-related, which did not become a loss to follow-up. Internal study validity was preserved with 31 subjects studied (group 1, $n = 15$; group 2, $n = 16$), in accordance with a sample size calculation of 15 subjects/group. Double or triple blinding was not applied, considering the tight exercise monitoring by physiotherapists.

The aerobic training intensity attained versus prescribed was 92% in group 1 and 82% in group 2. The reason for this might have been the strict length of the 8-week program as defined by the protocol. Moreover, clinical practice shows that many subjects attain the target intensity with longer programs. Although it was not the purpose of our study, future research should focus on the impact of different training intensities on physical activity of daily life as a meaningful patient-centered outcome.

Conclusions

Health-care providers acknowledge the level A recommendation of a pulmonary rehabilitation program with therapeutic exercise for all symptomatic patients with COPD. This study evidenced an equivalence effect of moderate and high intensities on HRQOL, symptom control, and exercise tolerance. The implication for clinical practice is that aerobic training intensity should be at least 60% W_{max} to achieve not only physiological benefits but also patient-centered outcomes, challenging the present clinical attitude of rehabilitation professionals. Continuing the present study, future research should address the impact of designing specific training activities related to the patient's real living environment and also the long-term effects on physical activity in daily life.

REFERENCES

1. Mathers C, Fat DM. The global burden of disease: 2004 update. World Health Organization, Geneva.
2. Respira. EFA: livro sobre a doença pulmonar obstrutiva crónica na Europa. In: Franchi M, editor. Lisbon, Portugal: Respira; Associação Portuguesa de Pessoas com DPOC e outras doenças respiratórias crónicas; 2010:132.
3. ERS Task Force, Palange P, Ward SA, Carlsen KH, Casaburi R, Gallagher CG, et al. Recommendations on the use of exercise testing in clinical practice. Eur Respir J 2007;29(1):185-209.
4. Hill NS. Pulmonary rehabilitation. Proc Am Thorac Soc 2006;3(1): 66-74.
5. Rodrigues F. [Limiting factors of exercise capacity in patients with COPD]. Rev Port Pneumol 2004;10(1):9-61. *Article in Portuguese.*
6. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, updated 2011. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Feb18.pdf.
7. American Association of Cardiovascular and Pulmonary Rehabilitation. Guidelines for pulmonary rehabilitation programs, 4th edition. Champaign, Illinois: American Association of Cardiovascular and Pulmonary Rehabilitation; 2013.
8. American Association for Respiratory Care. AARC clinical practice guideline: pulmonary rehabilitation. Respir Care 2002;37(5):617-625.
9. Ries AL. ACCP/AACVPR evidence-based guidelines for pulmonary rehabilitation. Round 3: another step forward. J Cardiopulm Rehabil Prev 2007;27(4):233-236.
10. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 2006;173(12):1390-1413.
11. Fahy BF. Pulmonary rehabilitation for chronic obstructive pulmonary disease: a scientific and political agenda. Respir Care 2004; 49(1):28-36; discussion 36-28.
12. Pierson DJ. Clinical practice guidelines for chronic obstructive pulmonary disease: a review and comparison of current resources. Respir Care 2006;51(3):277-288.
13. Gosselink R, Troosters T, Decramer M. Exercise training in COPD patients: the basic questions. Eur Respir J 1997;10(12):2884-2891.
14. Smidt N, de Vet HC, Bouter LM, Dekker J, Arendzen JH, de Bie RA, et al. Effectiveness of exercise therapy: a best-evidence summary of systematic reviews. Aust J Physiother 2005;51(2):71-85.
15. Maltais F, Hershfield E, Stubbing D, Wijkstra P, Hatzoglou A, Loveridge B, et al. Exercise training in patients with COPD. In: Bourbeau J, Nault D, Borycki E, editors. Comprehensive management of chronic obstructive pulmonary disease. Hamilton, Ontario, Canada: BC Decker; 2002.
16. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest 2007;131(5):4S-42S.

17. Troosters T, Donner C, Schols A, Decramer M. Rehabilitation in chronic obstructive pulmonary disease. European Respiratory Monograph. Wakefield, United Kingdom: European Respiratory Society; 2006;337-358.
18. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;172(1):19-38.
19. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013;188(8):e13-e64.
20. Jones PW, Quirk FH, Baveystock CM. The St George's respiratory questionnaire. Respir Med 1991;85(Suppl B):25-31; discussion 33-37.
21. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea: contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 1984;85(6):751-758.
22. Garrod R, Bestall JC, Paul EA, Wedzicha JA, Jones PW. Development and validation of a standardized measure of activity of daily living in patients with severe COPD: the London chest activity of daily living scale (LCADL). Respir Med 2000;94(6):589-596.
23. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166(1):111-117.
24. Cazzola M. ATS/ERS Task Force: outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008; 31(2):416-469.
25. Finch E, Brooks D, Stratford P, Mayo N. Physical rehabilitation outcome measures: a guide to enhanced clinical decision making. Hamilton, Toronto, Ontario, Canada: Lippincott, Williams & Wilkins; 2002.
26. Witek TJ Jr, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. Eur Respir J 2003;21(2):267-272.
27. Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil 2010;91(2):221-225.
28. Laviolette L, Bourbeau J, Bernard S, Lacasse Y, Pepin V, Breton MJ, et al. Assessing the impact of pulmonary rehabilitation on functional status in COPD. Thorax 2008;63(2):115-121.
29. Puente-Maestu L, Villar F, de Miguel J, Stringer WW, Sanz P, Sanz ML, et al. Clinical relevance of constant power exercise duration changes in COPD. Eur Respir J 2009;34(2):340-345.
30. Ferrer M, Villasante C, Alonso J, Sobradillo V, Gabriel R, Vilagut G, et al. Interpretation of quality of life scores from the St George's Respiratory Questionnaire. Eur Respir J 2002;19(3):405-413.
31. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription, 9th edition. Baltimore, MD: Lippincot Williams & Wilkins; 2013.
32. Lacasse Y, Martin S, Lasserson TJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease: a Cochrane systematic review. Eura Medicophys 2007;43(4):475-485.
33. Puhan MA, Schünemann HJ, Frey M, Scharplatz M, Bachmann LM. How should COPD patients exercise during respiratory rehabilitation? Comparison of exercise modalities and intensities to treat skeletal muscle dysfunction. Thorax 2005;60(5):367-375.
34. Bernard S, Whittom F, Leblanc P, Jobin J, Belleau R, Bérubé C, et al. Aerobic and strength training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159(3):896-901.
35. Pereira AM, Santa-Clara H, Pereira E, Simões S, Remédios I, Cardoso J, et al. Impact of combined exercise on chronic obstructive pulmonary patients' state of health. Rev Port Pneumol 2010;16(5): 737-757.
36. Montes de Oca M, Torres SH, González Y, Romero E, Hernández N, Tálamo C. Changes in exercise tolerance, health related quality of life, and peripheral muscle characteristics of chronic obstructive pulmonary disease patients after 6 weeks' training. Arch Bronconeumol 2005;41(8):413-418.
37. Dourado VZ, Tanni SE, Antunes LC, Paiva SA, Campana AO, Renno AC, Godoy I. Effect of three exercise programs on patients with chronic obstructive pulmonary disease. Braz J Med Biol Res 2009; 42(3):263-271.
38. Arnardóttir RH, Sörensen S, Ringqvist I, Larsson K. Two different training programmes for patients with COPD: a randomised study with 1-year follow-up. Respir Med 2006;100(1):130-139.
39. Foglio K, Bianchi L, Bruletti G, Porta R, Vitacca M, Balbi B, Ambrosino N. Seven-year time course of lung function, symptoms, health-related quality of life, and exercise tolerance in COPD patients undergoing pulmonary rehabilitation programs. Respir Med 2007; 101(9):1961-1970.
40. Normandin EA, McCusker C, Connors M, Vale F, Gerardi D, ZuWallack RL. An evaluation of two approaches to exercise conditioning in pulmonary rehabilitation. Chest 2002;121(4):1085-1091.
41. Rochester CL. Exercise training in chronic obstructive pulmonary disease. J Rehabil Res Dev 2003;40(5 Suppl 2):59-80.
42. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic-acidosis and ventilation as a result of exercise training in patients with obstructive lung-disease. Am Rev Respir Dis 1991;143(1):9-18.
43. Maltais F, LeBlanc P, Jobin J, Bérubé C, Bruneau J, Carrier L, et al. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997;155(2):555-561.
44. Puente-Maestu L, Sánz ML, Sánz P, Cubillo JM, Mayol J, Casaburi R. Comparison of effects of supervised versus self-monitored training programmes in patients with chronic obstructive pulmonary disease. Eur Respir J 2000;15(3):517-525.
45. Gimenez M, Servera E, Vergara P, Bach JR, Polu JM. Endurance training in patients with chronic obstructive pulmonary disease: a comparison of high versus moderate intensity. Arch Phys Med Rehabil 2000;81(1):102-109.
46. Hsieh MJ, Lan CC, Chen NH, Huang CC, Wu YK, Cho HY, Tsai YH. Effects of high-intensity exercise training in a pulmonary rehabilitation programme for patients with chronic obstructive pulmonary disease. Respirology 2007;12(3):381-388.
47. Butcher SJ, Jones RL. The impact of exercise training intensity on change in physiological function in patients with chronic obstructive pulmonary disease. Sports Med 2006;36(4):307-325.

ESTUDOS 8 a 10

IMPORTÂNCIA DA ATIVIDADE FÍSICA NA DPOC:

FATORES QUE INFLUENCIAM A ATIVIDADE FÍSICA DIÁRIA

EVOLUÇÃO DA CAPACIDADE FUNCIONAL E ESTADO DE SAÚDE DOIS ANOS APÓS UM PROGRAMA DE REABILITAÇÃO RESPIRATÓRIA

O PROJETO TELEMOLD: SISTEMA DE TELEMONITORIZAÇÃO QUE COMBINA A OXIMETRIA E A QUANTIFICAÇÃO DA ATIVIDADE FÍSICA PARA UMA MELHOR ADEQUAÇÃO DA OXIGENOTERAPIA DE LONGA DURAÇÃO

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ORIGINAL ARTICLE

Factors that influence physical activity in the daily life of male patients with chronic obstructive pulmonary disease☆

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KEYWORDS
Chronic obstructive pulmonary disease;
Activities of daily living;
Pedometer

Abstract
Introduction: Chronic obstructive pulmonary disease (COPD) is a disease with great impact on the ability to carry out physical activity.
Objective: To identify the main factors that affect physical activity in the daily life of patients with COPD.
Methods: Physical activity in daily routine has been evaluated according to the *London Chest Activity of Daily Living* scale (LCADL) and the pedometer counting the number of steps per day, for a period of three days. Fifty-five male patients with a diagnosis of moderate to very severe COPD were included (aged 67 ± 9.6 years; FEV_1 50.8 ± 14.7% predicted).
Results: Patients walked on average 4972 steps per day. Very severe COPD patients ($n = 12$) walked much less than severe ($n = 21$) and moderate ($n = 22$) patients (respectively 3079.8 versus 4853.5 and 6118.1 steps per day, $p < 0.001$). The number of steps per day had a negative correlation with age, dyspnea (mMRC), depression, BODE index and pulmonary hyperinflation; and a positive correlation with the distance covered in the six-minute walk test (6MWT), forced expiratory volume in the first second (FEV_1), carbon monoxide diffusion capacity (DLCO), arterial oxygen saturation (SpO_2) and body mass index (BMI).
Conclusions: The main factors that correlated with limited physical activity in daily life routine of this group of COPD patients were dyspnea and 6 min walking distance. These patients form a sedentary group, with a low rate of daily physical activity, which is more evident in patients with GOLD spirometry stage IV. Although pedometer is simpler and less accurate than other devices, it can be used to detect significant restraints daily life physical activity of COPD patients.

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PALAVRAS-CHAVE
Doença Pulmonar Obstrutiva Crónica;
Atividades da Vida Diária;
Pedómetro

Fatores que influenciam a atividade física na vida diária dos doentes do sexo masculino com doença pulmonar obstrutiva crónica

Resumo
Introdução: A Doença Pulmonar Obstrutiva Crónica (DPOC) é uma doença com grande impacto na capacidade de realizar atividade física.
Objetivo: Identificar os principais fatores que influenciam a atividade física na vida diária dos doentes com DPOC.
Métodos: A atividade física na rotina diária foi avaliada de acordo com a escala *London Chest Activity of Daily Living* (LCADL) e a quantificação do número de passos por dia avaliada com pedómetro durante um período de 3 dias. Foram selecionados 55 doentes do sexo masculino com o diagnóstico de DPOC moderada a muito grave (com 67±9,6 anos de idade e volume expiratório forçado no primeiro segundo (FEV1) 50,8±14,7% do previsto).
Resultados: Os doentes andaram uma média de 4.972 passos por dia. Os doentes com DPOC muito grave (n=12) andaram muito menos do que os doentes com DPOC grave (n=21) e moderada (n=22) (respetivamente, 3.079,8 versus 4.853,5 e 6.118,1 passos por dia, $p < 0,001$). O número de passos por dia apresentou uma correlação negativa com a idade, dispneia (mMRC), depressão, índice BODE e hiperinsuflação pulmonar; e apresentou uma correlação positiva com a distância percorrida na prova de marcha de seis minutos (6MWT), FEV1, capacidade de difusão do monóxido de carbono (DLCO), saturação de oxigénio arterial (SpO2) e índice de massa corporal (IMC).
Conclusões: Os principais fatores que se correlacionaram com a limitação da atividade física na rotina da vida diária deste grupo de doentes com DPOC foram a dispneia e a distância percorrida na prova de marcha dos 6 minutos. Estes doentes formam um grupo sedentário, com uma taxa reduzida de atividade física diária, o que é mais evidente em doentes com espirometria de estádio GOLD IV. Embora o pedómetro seja mais simples e menos preciso que outros dispositivos, pode ser usado para detetar restrições significativas da atividade física na vida diária dos doentes com DPOC.

Introduction

Monitoring of the daily physical activity in patients with COPD has been a subject of study, since physical activity is known to be reduced[1,2] due to multifactorial causes and worsened prognosis.

The present recommendations[3] point out the benefits of moderately intense daily physical activity for at least 30 min 5 times/week (or 150 min/week) and considers those not meeting this goal as insufficiently active.

Physical activity in daily life can be measured with pedometers,[4] which evaluate the vertical body movement, counting the number of steps during a certain period of time, during a recommended evaluation period of three days.[5] Although less accurate than accelerometers, these devices provide a low-cost objective measurement of walking, a daily physical activity responsible for a great amount of the total energy expenditure.

Tudor-Locke and Bassett[6] proposed the following indices of physical activity measured with a pedometer in adults: less than 5000 steps per day – ''sedentary''; 5000–7499 steps per day – ''low active''; 7500–10,000 steps per day – ''somewhat active'' and more than 10,000 steps per day – ''active''.

The main goal of this study was to identify the factors that influence physical activity in the daily life in COPD patients. Secondary goals were: (1) to find out whether there were differences in physical activity according to airways flow limitation (GOLD spirometry grade[7]); (2) to compare the number of steps per day measured with the pedometer and daily living activities (reported by London Chest of Activity Daily Living scale) and (3) to relate clinical, nutritional, psychological, lung function and exercise variables with daily living activities of COPD patients.

Methods

Sample

This study included 55 moderate to very severe[7] COPD patients, followed in the Pulmonology Unit and selected consecutively in a period of 7 months.

The inclusion criteria were: male sex; smoking history above 10 pack-years; COPD diagnosis; $FEV_1/FVC\%$ ratio less than 70% and FEV_1 less than 80% of predicted post-bronchodilation and stable disease (absence of exacerbation or change in treatment in the last three months). Exclusion criteria were other conditions that could also cause or enhance dyspnea (e.g. asthma, cardiovascular diseases), conditions that could impair physical activity performance (e.g. cerebrovascular, osteoarticular or psychiatric diseases) or already taking part in a pulmonary rehabilitation program.

The study was carried out at the Respiratory Physiopathology Laboratory, Centro Hospitalar de Torres Vedras, after being approved by the Centro Hospitalar de Torres Vedras Ethics Committee, and after obtaining written informed consent from the patients.

Characterization of the sample

Patients were clinically evaluated, including their smoking habits and the modified *Medical Research Council* (mMRC) dyspnea scale quantification. mMRC is formed by 5 grades (0 to 4), the highest value corresponding to the greatest limitation caused by dyspnea in the activities of daily life.[8]

Anxiety and depression were investigated using the hospital anxiety and depression scale (HADS). This scale is composed of 14 items, 7 being related to anxiety and 7 to depression, with a maximum possible score of 21 for every quotation.[9]

The nutritional assessment was based on the body mass index (BMI) evaluation, defined as the weight in kilos divided by the height in squared meters. According to the adopted reference values,[10] a BMI below 20 kg/m^2 was considered low weight, from 20 to 24.9 kg/m^2 normal weight, from 25 to 29.9 kg/m^2 overweight and obesity from 30 kg/m^2.

Pulmonary function tests at rest included spirometry with bronchodilation test, evaluation of pulmonary static volumes by plethysmography and carbon monoxide diffusion capacity by the single breath method (Sensor Medics, model AutoBox Vmax 22, Yorba Linda, CA, USA, for all lung tests) according to the standard methods.[11,12,13]

Two 6MWT were performed according to the standard methods[14] with a minimum interval of 30 min between them. The one with the longest distance covered was chosen. Arterial blood gases were assessed at the beginning and at the end of the 6MWT (Gas analyser Elnor Nova Biomedical Stat Profile pHOx Plus/c, Waltham, USA). Oxygen saturation by pulse oximetry and dyspnea by the modified Borg scale[15] were also evaluated at rest, in the beginning and immediately after 6MWT.

At the end of these evaluations, the BODE index was calculated.[16]

Evaluation of physical activity in daily life

Physical activity in daily life was evaluated according to LCADL scale and the number of steps per day, on three consecutive days, between Monday and Friday, was counted using the pedometer.

LCADL contains 15 activities of daily living (ADL) items, divided into four sections (self-care, domestic, physical and leisure), where the patients give to each item a score from 0 to 5, mentioning to what extent dyspnea interferes with these 15 activities. It is possible to get a total score of between 0 and 75. The higher the results on the scale the greater the limitation in ADL.[17,18]

After completing the scale, a pedometer *Geonaute Dista T300* was given to each patient, who then placed it on their waistband when walking (pedometer had to be removed each time the patient takes a shower, lies in bed or in any other situation which might damage the gear), keeping to their daily routine for three days.

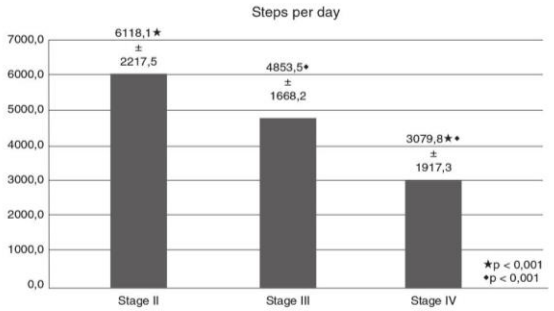

Figure 1 Average number of steps per day.

Statistical analysis

Data are expressed as mean ± standard deviation (SD).

ANOVAs one-way test was used, followed by tests of multiple a posteriori comparisons of Tukey to assess the differences in physical activity in daily life according to flow limitation (GOLD spirometry grade).

We compared the number of steps per day measured with the pedometer and LCADL through the Spearman correlation coefficient. The number of steps per day was a dependent variable. The independent variable selection was achieved by Pearson's correlation coefficient analysis.

Finally, a stepwise multiple linear regression analysis was done, in order to estimate the influence of the variables on physical activity in the daily routine, according to the pedometer. The level of significance was set at $p < 0.05$.

All analysis was done with SPSS v.16.0 software (Statistical Package for the Social Sciences) for Mac.

Results

The clinical, nutritional, psychological, lung function features as well as features of physical activity of the sample are shown in Table 1.

In the evaluation of daily life activities using the LCADL scale, there were differences with statistical relevance between the very severe patients (grade IV) and the patients with moderate COPD (grade II), with the former showing, on average, a higher total score in the LCADL scale (20.8 ± 5.1 versus 15.9 ± 3.6, $p < 0.027$).

The evaluation of physical activity in daily life measured with pedometer in all groups of patients showed that the average number of steps per day was 4972.4, distributed through different stages of the disease according to Fig. 1. There were statistical differences between patients with COPD spirometry stage IV and patients with stages II and III, the very severe patients being those who walk less (on average 3079.8 versus 4853.5 and 6118.1 steps per day, $p < 0.001$).

Examining the linear correlation coefficients (Table 2), the number of steps per day has shown a negative correlation with age, dyspnea, depression, BODE index, pulmonary hyperinflation and LCADL; it is positively correlated with the distance covered and with minimal oxygen saturation in 6MWT, FEV_1, DLCO, and BMI.

Table 1 Clinical, nutritional, psychological, respiratory function and physical activity characterization.

	GOLD II ($n=22$)	GOLD III ($n=21$)	GOLD IV ($n=12$)	($n=55$)
Age (years)	67.0 ± 12.2	67.9 ± 6.8	66.1 ± 8.6	67.2 ± 9.6
Smoking history (pack-years)	54.8 ± 26.7	53.0 ± 26.7	65.0 ± 22.1	56.4 ± 25.7
BMI ($kg\,m^{-2}$)	28.1 ± 3.2	28.6 ± 4.6	26.0 ± 5.1	27.8 ± 4.2
mMRC dyspnea	1.9 ± 0.6	2.4 ± 1.1	3.3 ± 1.0	2.4 ± 1.0
Depression total score	5.7 ± 2.8	5.1 ± 2.4	7.2 ± 3.3	5.8 ± 2.8
Anxiety total score	6.6 ± 2.4	6.8 ± 3.5	7.0 ± 2.0	6.8 ± 2.8
BODE index	1.8 ± 1.2	3.9 ± 1.4	5.9 ± 1.5	3.5 ± 2.1
Pulmonary function				
FEV_1 (% predicted)	66.6 ± 8.0	42.3 ± 4.9	36.9 ± 6.9	50.8 ± 14.7
FVC (% predicted)	92.4 ± 9.0	70.3 ± 13.9	70.0 ± 17.0	79.1 ± 16.8
FEV_1/FVC (%)	56.8 ± 8.6	48.5 ± 8.7	43.0 ± 10.8	50.6 ± 10.5
TLC (% predicted)	110.6 ± 13.4	107.5 ± 14.6	117.3 ± 16.4	110.9 ± 14.8
RV (% predicted)	153.8 ± 42.1	172.7 ± 34.4	196.6 ± 36.5	170.4 ± 40.8
RV/TLC (%)	53.1 ± 11.4	61.9 ± 8.2	65.8 ± 5.7	59.2 ± 10.5
DLCO (% predicted)	72.7 ± 24.2	63.5 ± 22.1	47.8 ± 16.5	63.8 ± 23.5
DLCO/VA (% predicted)	69.5 ± 17.4	71.9 ± 17.6	52.1 ± 15.8	66.6 ± 18.6
PaO_2 (mmHg)	79.5 ± 9.5	78.8 ± 8.0	65.7 ± 7.7	76.2 ± 10.1
$PaCO_2$ (mmHg)	39.4 ± 3.6	41.0 ± 3.4	40.1 ± 3.9	40.2 ± 3.6
Exercise capacity				
6MWD (m)	391 ± 85.7	370 ± 72.7	268 ± 94.7	356 ± 94.5
SpO_2 minimal (%)	88.4 ± 5.6	87.3 ± 5.4	79.5 ± 7.0	86.0 ± 6.7
Initial dyspnea (Borg)	0.2 ± 0.5	0.3 ± 0.7	1.3 ± 1.2	0.5 ± 0.9
Final dyspnea (Borg)	1.3 ± 0.9	1.9 ± 1.3	3.4 ± 1.2	2.0 ± 1.4
Final HR (bpm)	114.8 ± 20.7	127.3 ± 14.6	131.1 ± 24.3	123.2 ± 20.4
LCADL total score	15.9 ± 3.6⊗	17.8 ± 5.8	20.8 ± 5.1⊗	17.7 ± 5.1
Steps/day	6118.1 ± 2217.5*	4853.5 ± 1668.2♦	3079.8 ± 1917.3*♦	4972.4 ± 2242.3

BMI: body mass index; mMRC dyspnea: modified *Medical Research Council dyspnea scale*; BODE: BODE index (B: body mass index; O: obstruction; D: dyspnea; E: exercise); FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; DLCO: carbon monoxide diffusion capacity; DLCO/VA: DLCO corrected to alveolar volume; PaO_2: arterial oxygen pressure; $PaCO_2$: carbon dioxide arterial pressure; 6MWD: six-minute walk distance; SpO_2: arterial oxygen saturation; HR: heart rate; bpm: beat per minute.
Values are shown as mean ± SD. Respiratory failure patients were classified as GOLD IV.
⊗ $p<0.027$.
*♦ $p<0.001$.

In order to test the contribution of every variable to explain the variance with the number of steps per day in the patients with COPD studied, we set a stepwise multiple regression analysis, so as to eliminate redundant variables. To this effect, all variables that had shown relevant correlations in the simple linear correlation analysis were included in the multiple regression analysis.

As a result, we got a model where the significant variables that helped to explain the number of steps per day (64.2% of its variance – $R^2=0.642$) were dyspnea (mMRC) and the distance covered in 6MWT (Table 3).

Discussion

In this study we identified the key factors related to physical activity in the daily life of a group of COPD patients at GOLD spirometry stage II to IV. These factors were dyspnea and the distance covered in 6MWT. Moreover, in our sample, there were differences between patients with stage IV and patients with moderate and severe COPD (stages II and III), the most severe cases being those patients who walk less in their daily routine (3079.8 steps per day) when compared to less severe patients (4853.5 steps per day) and the moderate ones (6118.1 steps per day). Even our moderate COPD patients are markedly sedentary, which classifies them as low active, as set out by Tudor-Locke and Bassett.[6]

Watz et al.[19] also verified a larger reduction in COPD patients' daily life physical activity according to the severity of the disease, but present at all COPD stages, compared to chronic bronchitis patients.

In relation to LCADL scale, there were significant differences between COPD stage IV (20.8) and COPD stage II patients (15.9); the most severe patients were those who showed greater restrictions during activities of daily living.

Comparing the pedometer and LCADL scale, we verified a negative and moderate correlation ($r=-0.499$; $p<0.01$) showing that the higher the ADL restraint, the lower the daily physical activity in these patients, assessed by the number of steps per day.

Among the factors that can limit physical activity in daily life, dyspnea is known to be rather variable in this population and its origin is recognized as multifactorial.[20]

Table 2 Linear correlation coefficients.

Variable	*r*	*p*
Age	−0.416	$p < 0.01$
BMI	0.276	$p < 0.05$
mMRC dyspnea	−0.661	$p < 0.01$
BODE	−0.741	$p < 0.01$
Depression total score	−0.424	$p < 0.01$
LCADL	−0.499	$p < 0.01$
FEV_1	0.493	$p < 0.01$
RV	−0.336	$p < 0.05$
DLCO	0.551	$p < 0.01$
6MWD	0.719	$p < 0.01$
Minimal SpO_2	0.633	$p < 0.01$
Dyspnea (Borg)	−0.601	$p < 0.01$

BMI: body mass index; mMRC dyspnea: modified *Medical Research Council dyspnea scale*; BODE: BODE index (B: body mass index; O: obstruction; D: dyspnea; E: exercise); LCADL: *London Chest Activity of Daily Living scale*; FEV_1: forced expiratory volume in one second; RV: residual volume; DLCO: carbon monoxide diffusion capacity; 6MWD: six minute walk distance; SpO_2: arterial oxygen saturation.

Table 3 Multiple regression analysis.

$R^2 = 0.642$	β	*p* value
mMRC dyspnea	−0.406	<0.001
6MWD	0.520	<0.001

The present study found a negative and moderate correlation ($r = -0.661$; $p < 0.01$) between dyspnea (mMRC) and the number of steps per day, and it was one of the main factors that contributed to its variance ($\beta = -0.406$, $p < 0.001$), reflecting the effect of the downward spiral of COPD, derived from the interaction of dyspnea, inactivity and physical deconditioning, since the higher the dyspnea is, the higher the ADL restraint and the lower the number of steps per day will be. Dyspnea assessed on the Borg scale was also negatively correlated with the number of steps per day, suggesting that the degree of dyspnea developed in the walk test is similar to the one realized in ADL evaluated by mMRC scale.[21]

Another determining factor for the variation of the number of steps per day was the distance covered in 6MWT ($\beta = 0.520$, $p < 0.001$). The high linear association between the daily physical activity assessed with the pedometer and the distance covered in 6MWT ($r = 0.719$; $p < 0.001$) suggests that the pedometer gives a valid measurement of physical activity in this group with functional restraint, quantifying walking, which is the most common and available physical activity modality and seems to strongly contribute to the level of total daily physical activity.[22] Furthermore, this close relationship between the pedometer and 6MWT is comparable to what Fabio Pitta et al. also showed: the distance covered by 6MWT (functional exercise) has a high correlation with the physical activity level that patients develop in daily life.[1] In Pitta's study, activity was also positively related to accelerometer data, showing that a reduction in the distance covered in 6MWT is the best marker of inactivity during the daily life of patients with COPD.

In this study, FEV_1 was related in a positive and moderate way to the number of steps per day ($r = 0.493$; $p < 0.01$), as is also referred to in other studies.[1,2,19] Other authors, however, have not found any correlation between physical activity and the severity of COPD, probably owing to differences in the degree of obstruction, sample size and the instruments used to assess physical activity in daily routine.[23–26]

As also mentioned in other papers,[27–31] most of the patients in this sample (80%) showed pulmonary hyperinflation at rest. As one of the most important factors associated with dyspnea in patients with COPD, in our study, pulmonary hyperinflation also showed a negative and moderate correlation with the daily physical activity assessed by the pedometer ($r = -0.511$; $p < 0.01$). However, it did not contribute to the variance in the number of steps per day in the multiple regression analysis.

Concerning gas exchanges, DLCO was positively correlated with the number of steps per day. Other authors[32,33] also found a significant contribution of DLCO to the physical activity performance of COPD patients.

In this study, 76% of the patients showed arterial oxygen desaturation during the 6MWT and the minimal SpO_2 correlated positively with the number of steps per day ($r = 0.633$; $p < 0.01$)

Age was negatively correlated ($r = -0.416$; $p < 0.01$) with the level of physical activity registered by the pedometer, suggesting that older people are less active, walking fewer steps per day, as has already been shown.[34]

BMI was associated in a positive, significant and weak way ($r = 0.276$; $p < 0.05$) to the number of steps per day, as also shown in other studies.[2,35]

The BODE index showed a negative and strong correlation with the number of steps per day ($r = -0.741$; $p < 0.01$). However, in the model of multiple linear regressions, its influence on the variance of the number of steps per day loses statistical relevance.

Psychological factors, such as anxiety and depression, have been described as frequent in these patients, contributing to a lower level of physical activity, even after well structured pulmonary rehabilitation programs. In this sample, the prevalence found was much lower than in other studies,[36–39] but depression was correlated in a negative but moderate way with the number of steps per day ($r = -0.424$; $p < 0.01$). Besides dyspnea and exercise capacity, psychological factors such as anxiety and depression, behavioral factors such as lack of motivation and self-efficacy, and social and environmental barriers are all capable of influencing physical activity and further studies should be directed at their identification and management.

There are some limitations to consider in this study. Since the sample only included male patients, we cannot apply the results to the female population. Although the prevalence of COPD is increasing in women, in Portugal it is still much more prevalent in men [18.7 versus 10.5% – Bárbara et al.[43]]. When recruiting patients for this study, there were so few COPD female patients that it would not have been possible to generalize the conclusions from these gender patients. Moreover, if there had been a control group it would have allowed us to compare the patients with another patient population group or to healthy people, thus marking their level of daily physical activity.

In this study the LCADL scale showed a low average total score (17.7), probably because the sample was formed by a male population, 73% of which stated they did not do any kind of household tasks, or because most of the patients underestimated the severity of their disease.[18,39–42] While most of them considered themselves as suffering from a light dyspnea, their average number of steps per day was low, showing how inactive they are in their daily lives.

Concerning pedometer data, it is not possible to control possible sources of error, such as low walking speed, forgetting or incorrectly setting the equipment or vibrations, e.g. when driving a car or a bicycle. These errors are assumed to have been reduced by keeping with a three-day record, as recommended.[5] As was demonstrated by Van Remoortel et al. in a recent systematic review (PROactive consortium), uniaxial pedometers are significantly less accurate than multisensor devices, particularly at slow walking speeds.[44] Therefore the results of our study should be treated cautiously.

In conclusion, the main factors that contributed to physical activity restraint in male COPD patients daily life assessed with a pedometer were dyspnea (mMRC) and the low functional exercise capacity (distance covered in the 6MWT). These results point to the need for a better control of these two issues in clinical practice. These patients are markedly inactive and show limitations in ADL, becoming these features more evident in patients with very severe COPD.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received sufficient information and gave their written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Pitta F, Troosters T, Spruit M, Probst V, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;171:972–7.
2. Schonhofer B, Ardes P, Geibel M, Kohler D, Jones PW. Evaluation of a movement detector to measure daily activity in patients with chronic lung disease. Eur Respir J. 1997;10:2814–9.
3. Haskell W, Lee I, Pate R, Powell K, Blair S, Franklin B, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007;39:1423–34.
4. Pitta F, Troosters T, Spruit M, Probst V, Decramer M, Gosselink R. Quantifying physical activity in daily life with questionnaires and motion sensors in COPD. Eur Resp J. 2006;27:1040–55.
5. Tudor-Locke C, Burkett L, Reis JP, Ainsworth BE, Macera CA, Wilson DK. How many days of pedometer monitoring predict weekly physical activity in adults? Prev Med. 2005;40:293–8.
6. Tudor-Locke C, Bassett D. How many steps/day are enough? Preliminary pedometer indices for public health. Sports Med. 2004;34:1–8.
7. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; 2008.
8. Bestall J, Paul E, Garrod R, Garnham R, Jones P, Wedzicha J. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54:581–6.
9. Zigmond A, Snaith R. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70.
10. ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23:932–46.
11. ATS/ERS Task Force: Standardisation of Lung Function Testing. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.
12. ATS/ERS Task Force: Standardisation of Lung Function Testing. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26:511–22.
13. ATS/ERS Task Force: Standardisation of Lung Function Testing. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26:720–35.
14. American Thoracic Society. ATS Statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111–7.
15. Borg G. Borg's perceived exertion and pain scales. Human Kinetics. Copyright © 1998 by Gunnar Borg. ISBN 0-88011-623-4.
16. Celli B, Cote C, Marin J, Casanova C, Oca M, Mendez R, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005–12.
17. Garrod R, Bestall J, Paul E, Wedzicha J, Jones P. Development and validation of a standardized measure of activity of daily living in patients with severe COPD: the London Chest Activity of Daily Living scale (LCADL). Respir Med. 2000;94:589–96.
18. Pitta F, Probst V, Kovelis D, Segretti N, Leoni A, Garrod R, et al. Validação da versão em português da escala London Chest Activity of Daily Living (LCADL) em doentes com doença pulmonar obstructiva crónica. Rev Port Pneumol. 2008;XIV:27–47.
19. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. Eur Respir J. 2009;33:262–72.
20. American Thoracic Society. Dyspnea. Mechanisms, assessment and management: a consensus statement. Am J Respir Crit Care Med. 1999;159:321–40.
21. Gallego M, Samaniego J, Alonso J, Sanchez A, Carrizo S, Marin J. Dyspnea in COPD: relation to the MRC scale with dyspnea induced by walking and cardiopulmonary stress testing. Arch Bronconeumol. 2002;38:112–6.
22. Cyarto E, Myers A, Tudor-Locke C. Pedometer accuracy in nursing home and community-dwelling older adults. Med Sci Sports Exerc. 2004;36:205–9.
23. Carter R, Holiday D, Nwasuruba C, Stocks J, Grothues C, Tiep B. 6-Minute walk work for assessment of functional capacity in patients with COPD. Chest. 2003;123:1408–15.
24. Casaburi R. Activity monitoring in assessing activities of daily living. COPD: J Chron Obstruct Pulmon Dis. 2007;4:251–5.
25. Wegner R, Jorres R, Kirsten D, Magnussen H. Factor analysis of exercise capacity, dyspnoea ratings and lung function in patients with severe COPD. Eur Respir J. 1994;7:725–9.

26. Wijkstra P, Vergert E, Marck T, Postma D, Altena R, Kraan J, et al. Relation of lung function, maximal inspiratory pressure, dyspnoea, and quality of life with exercise capacity in patients with chronic ostructive pulmonary disease. Thorax. 1994;49:468–72.
27. Casaburi R, Porszasz J, Burns M, Carithers E, Chang R, Cooper C. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;155:1541–51.
28. Engstrom C, Persson L, Larsson S, Ryden A, Sullivan M. Functional status and well being in chronic obstructive pulmonary disease with regard to clinical parameters and smoking: a descriptive and comparative study. Thorax. 1996;51:825–30.
29. Freitas C, Pereira C, Viegas C. Inspiratory capacity, exercise limitation, markers of severity, and prognostic factors in chronic obstructive pulmonary disease. J Bras Pneumol. 2007;33:389–96.
30. Marin J, Carrizo S, Gascon M, Sanches A, Gallego B, Celli B. Inspiratory capacity, dynamic hyperinflation, breathlessness, and exercise performance during the 6-minute walk test in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;163:1395–9.
31. O'Donnell D, Revill S, Webb K. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164:770–7.
32. Pereira A, Santa-Clara H, Pereira E, Simões S, Remédios I, Cardoso J, et al. Impacto do exercício físico combinado na percepção do estado de saúde da pessoa com doença pulmonar obstructiva crónica. Rev Port Pneumol. 2010;XVI:737–57.
33. Ringbaek T, Lange P. Outdoor activity and performance status as predictors of survival in hypoxaemic chronic obstructive pulmonary disease (COPD). Clin Rehabil. 2005;19:331–8.
34. Tudor-Locke C, Ham S, Macera C, Ainsworth B, Kirtland K, Reis J, et al. Descriptive epidemiology of pedometer-determined physical activity. Med Sci Sports Exerc. 2004;36:1567–73.
35. Tudor-Locke C, Ainsworth B, Whitt M, Thompson R, Addy C, Jones D. The relationship between pedometer-determined ambulatory activity and body composition variables. Intern J Obesity. 2001;25:1571–8.
36. Van Ede L, Yzermans C, Brouwer H. Prevalence of depression in patients with chronic obstructive pulmonary disease: a systematic review. Thorax. 1999;54:688–92.
37. Breslin E, Van der schans C, Breukink S, Meek P, Mercer K, Volz W, et al. Perception of fatigue and quality of life in patients with COPD. Chest. 1998;114:958–64.
38. Olsson I, Mykletun A, Dahl A. The hospital anxiety and depression rating scale: a cross-sectional study of psychometrics and case finding abilities in general practice. BMC Psychiatry. 2005;5:46–52.
39. Yohannes A, Roomi J, Baldwin R, Connolly M. Depression in elderly outpatients with disabling chronic obstructive pulmonary disease. Age Ageing. 1998;27:155–60.
40. Alvarez-Gutierrez F, Miravitlles M, Calle M, Gobartt E, Lopez F, Martin A, on behalf of EIME Study Group. Impact of chronic obstructive pulmonary disease on activities of daily living: results of the multicenter EIME study. Arch Bronconeumol. 2007;43:64–72.
41. Garrod R, Paul EA, Wedzicha JA. An evaluation of the reliability and sensitivity of the London Chest Activity of Daily Living Scale (LCADL). Respir Med. 2002;96:725–30.
42. Simon KM. Atividade de vida diária e índice de mortalidade ''BODE'' em indivíduos portadores de doença pulmonar obstrutiva crónica. Uberlândia: Dissertação apresentada ao programa de mestrado em fisioterapia; 2006.
43. Bárbara C, Rodrigues F, Dias H, Cardoso J, Almeida J, Matos MJ, et al. COPD prevalence in Lisbon, Portugal: the Burden of Obstructive Lung Disease. Rev Port Pneumol. 2013;19:96–105.
44. Van Remoortel H, Giavedoni S, Raste Y, Burtin C, Louvaris Z, Gimeno-Santos E, et al., on behalf of PROactive Consortium. Validity of activity monitors in health and chronic disease: a systematic review. Int J Behav Nutr Phys Act. 2012;9:84. http://www.ijbnpa.org/content/9/1/84

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ARTIGO ORIGINAL

Evolução da capacidade funcional e estado de saúde dois anos após um programa de reabilitação respiratória

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PALAVRAS-CHAVE
Reabilitação pulmonar;
Exercício;
Estado de saúde;
DPOC grave

Resumo
Introdução: Os programas de reabilitação respiratória (PRR) têm demonstrado em doentes com patologia pulmonar crónica, melhoria da capacidade de exercício e do estado de saúde e diminuição da dispneia e da utilização de recursos de saúde. Habitualmente, estes benefícios diminuem após conclusão dos programas.
Objetivo: Avaliar a capacidade funcional e o estado de saúde 2 anos após o término de um PRR.
Métodos: Estudo retrospetivo de doentes que completaram um PRR. Após o PRR, os doentes que referiam ter adotado um estilo de vida fisicamente ativo foram incluídos no grupo ativo (GA). Os restantes doentes foram considerados como grupo controlo (GC). A capacidade funcional foi avaliada com a prova de marcha dos 6 minutos (PM6m) e o estado de saúde com o questionário de St. George na doença respiratória (SGRQ).
Resultados: Foram incluídos 32 doentes, 24 no GA e 8 no GC. Imediatamente após o PRR observou-se, em ambos os grupos, uma melhoria significativa na PM6m e na pontuação total do SGRQ. Após o término do PRR, no GA, observou-se um declínio na distância média percorrida na PM6m aos 6 meses, 1 ano e 2 anos, bem como no estado de saúde.
Contudo, 2 anos após o PRR e comparando com os valores avaliados antes do início do PRR, o GA continuava a apresentar uma melhoria na distância percorrida na PM6m, em média de 32 m ($p = 0,03$) e de pelo menos 4 pontos no SGRQ. No GC observou-se um declínio clinicamente significativo na PM6m (−34 m) e no SGRQ (agravamento de 13 pontos).
Conclusão: Embora se verifique uma perda progressiva dos benefícios do PRR após a sua cessação, estes ainda são significativamente positivos até 2 anos após o treino no GA. Um estilo de vida fisicamente ativo parece contribuir para manter os benefícios do Programa de Reabilitação.

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KEYWORDS
Pulmonary rehabilitation;
Exercise;
Health status;
Severe COPD

Evolution of functional capacity and health status two years after a pulmonary rehabilitation programme

Abstract
Background: Pulmonary rehabilitation programs (PRP) have been shown to improve exercise capacity and health status and to reduce dyspnoea and use of healthcare resources, in patients with chronic lung disease. These benefits usually wane after the programs conclusion.
Aim: Evaluate functional capacity and health status 2 years after the end of a PRP.
Methods: Retrospective study of patients who took part in PRP. After PRP, patients who reported a physically active lifestyle were included in the active group (AG). The other patients were considered as the control group (CG). Functional capacity was evaluated with 6 minute walk distance (6MWD) and health status with St George's Respiratory Questionnaire (SGRQ).
Results: Thirty-two patients were included, 24 in the AG and 8 in the CG. Immediately after PRP, there was a significant improvement in the 6MWD and SGRQ global score, for both groups. After completing PRP, in the AG, there was a decline in the mean 6MWD when evaluated at 6 months, 1 and 2 years and also in health status.
However, after 2 years, the AG continued to show an average improvement of 32 m (p=0.03) in the 6MWD and at least 4 points in SGRQ compared to pre-PRP, while in the CG, there was a clinically significant decline in 6MWD (−34 m) and SGRQ score (13 points worse).
Conclusion: Despite the progressive decline of benefits gained after completing PRP, in the AG these are still significantly positive after 2 years. An active lifestyle seems to help maintain the benefits of the Rehabilitation Program.

Introdução

Existe uma forte evidência científica documentando a eficácia dos programas de reabilitação respiratória (PRR) em doentes com doença pulmonar crónica, em particular com DPOC[1–5].

Os PRR com uma duração de pelo menos 8 semanas de treino de exercício têm demonstrado melhorar a capacidade de exercício, o estado de saúde, a dispneia e reduzir a utilização de cuidados de saúde[6,7]. Após a fase intensiva do programa, estes benefícios tendem a diminuir[7].

Tendo em consideração o princípio da reversibilidade, após conclusão do treino de exercício[3,8] é necessário implementar estratégias para manter os benefícios do PRR, especialmente através da melhoria a longo prazo da capacidade de autogestão e aderência à prática de exercício no domicílio[9].

Várias estratégias têm sido desenvolvidas para manter os benefícios do PRR, tais como chamadas telefónicas, grupos de apoio, visitas regulares ao centro de reabilitação, visitas domiciliárias regulares e monitores de atividade[7,9,10]. Contudo os resultados destas intervenções variam entre os estudos.

O objetivo deste estudo foi avaliar a capacidade funcional e o estado de saúde aos 6 meses, 1 ano e 2 anos após a conclusão de um PRR, em doentes seguidos regularmente num hospital de dia de insuficientes respiratórios e avaliar uma potencial relação entre a manutenção da atividade física e os resultados obtidos no *follow up*.

Métodos

Amostra

Foram incluídos os doentes que participaram num programa de reabilitação respiratória no hospital de dia de insuficientes respiratórios do Hospital Pulido Valente, desde Setembro de 2005 a Fevereiro de 2010. Como critérios de inclusão os doentes deveriam ter completado o PRR e aceitar participar no programa de *follow up*.

Desenho do estudo

Os programas de reabilitação tinham uma duração de pelo menos 12 semanas e eram compostos por treino de exercício (tapete ou bicicleta, 3 vezes por semana) com intensidade alvo de 80% da potência de pico atingida durante um teste de exercício incremental máximo, realizado previamente no mesmo ergómetro. A duração do programa era a necessária para o doente atingir a intensidade alvo de 80% da potência de pico. Alguns doentes tiveram uma progressão mais lenta, devido aos sintomas e alguns tiveram de interromper o programa por exacerbações, mas retomaram-no logo que possível.

A modalidade do treino foi adaptada à preferência do doente e de acordo com a probabilidade do doente manter este exercício após terminar o PRR.

Todos os doentes receberam sessões educacionais e estratégias de promoção de competências de autogestão e,

se necessário, apoio psicológico e nutricional, bem como outros exercícios supervisionados (p. ex. exercícios respiratórios e treino dos membros superiores). Ao longo do programa, os doentes eram encorajados a adotar um estilo de vida ativo. Seis meses após o PRR, os doentes eram questionados sobre o seu nível de atividade física habitual. Se reportassem praticar exercício regularmente, de acordo com a prescrição (p. ex. pelo menos 30 minutos de caminhada ou exercício numa bicicleta estacionária, 3 vezes por semana) eram incluídos no grupo ativo (GA). Se pelo contrário voltassem a ser sedentários, eram considerados como grupo controlo (GC). Ambos os grupos eram incentivados, em cada visita semestral, a praticar exercício regularmente.

Os processos clínicos dos doentes que cumpriam os critérios de inclusão foram revistos e analisados os dados demográficos, hábitos tabágicos, doença pulmonar, comorbilidades (Índice de Charlson[11–13]), níveis de ansiedade e depressão (avaliados pela *Hospital Anxiety and Depression Scale*[14]), escala de dispneia do *Medical Research Council* (MRC)[15], provas funcionais respiratórias, duração do PRR, intensidade alvo atingida durante o PRR, prova de marcha dos 6 minutos (PM6m)[16] e o questionário de St. George na doença respiratória (SGRQ)[17]. A todos os doentes foi atribuído um código, a fim de manter a confidencialidade.

A PM6m foi realizada de acordo com as recomendações da *American Thoracic Society*[16]. Para superar o efeito de aprendizagem, a PM6m foi realizada inicialmente 3 vezes e a terceira foi considerada como a PM6m basal. O nosso protocolo incluía a realização da PM6m antes do PRR (basal), imediatamente após o PRR, aos 6 meses, 1 ano e 2 anos. Considerámos 25 metros como a distância mínima clinicamente significativa, como foi recentemente evidenciado por Holland et al.[18]

O SGRQ é um questionário estandardizado de autopreenchimento, utilizado para avaliar o estado de saúde em doentes com doença respiratória. Uma pontuação de zero indica o melhor resultado e cem, o pior[17,19]. O SGRQ foi realizado antes do PRR, imediatamente após o PRR, 1 ano e 2 anos após o PRR. Considerámos 4 pontos como a diferença mínima clinicamente significativa, de acordo com o autor Paul Jones[19].

Análise estatística

Os dados são apresentados como média ± desvio-padrão para as variáveis contínuas e como frequências e percentagens para as variáveis categóricas.

Todas as variáveis foram testadas para a distribuição normal através do histograma de frequência e os testes *Kolmogorov-Smirnov* ou *Shapiro-Wilk*. A diferença entre duas médias foi determinada utilizando o teste *T-Student* ou de *Mann-Whitney*, quando apropriado.

As proporções e variáveis categóricas foram analisadas com o teste do Qui-quadrado ou de *Fisher*, quando apropriado. Foi considerado um p estatisticamente significativo se inferior a 0,05.

A análise estatística foi realizada utilizando o software PASW (versão 18; SPSS Inc., Chicago, IL, EUA).

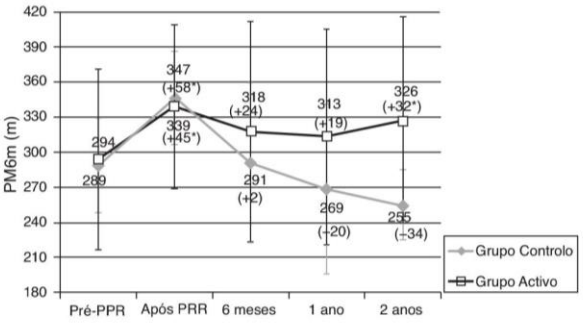

Figura 1 Resultados da prova de marcha dos 6 minutos (PM6m). Dados apresentados em média ± desvio padrão.
PRR: programa de reabilitação respiratória. * Melhoria significativa após reabilitação (p < 0,05). Diferença (em metros) Após-Pré PRR aparece entre parêntesis.
Dimensão da amostra: 24, 24, 19, 16, 16 para pré-PRR, após PRR, 6 meses, 1 ano e 2 anos, respectivamente no grupo activo; 8, 8, 6, 7, 4 para pré-PRR, após PRR, 6 meses, 1 ano e 2 anos, respetivamente no grupo controlo.

Resultados

Foram incluídos no estudo 32 doentes, 84,4% do género masculino, com média etária de 66,8 ± 9,4 anos. A maior parte dos doentes eram ex-fumadores (90,6%) e tinham o diagnóstico de DPOC (81,2%). Dos doentes com DPOC houve um predomínio do estádio IV do GOLD (80,8%).

A duração média do PRR foi de 26 semanas e todos os doentes atingiram a intensidade alvo (80% da potência de pico, avaliada previamente). A maioria dos doentes treinou em tapete (65,6%) e 34,4% em cicloergómetro.

Foram incluídos 24 doentes no grupo ativo (GA) e 8 doentes no grupo controlo (GC). As características basais eram semelhantes entre os grupos (tabela 1), com exceção de maior hipoxémia (58,8 *versus* 63,3 mmHg, p = 0,023) e maior número de comorbilidades no GC. No GA o número médio de comorbilidades era de 1,9 e as mais frequentes foram as doenças cardiovasculares (41,7%), seguido da dislipidémia (20,8%) e diabetes (16,7%). Os doentes do GC tinham em média 3 comorbilidades, sendo as mais frequentes as doenças cardiovasculares (75%) e a síndrome da apneia obstrutiva do sono (62,5%) (tabela 1).

Os doentes do GA e GC tiveram resultados semelhantes na PM6m e no SGRQ, antes do PRR (tabela 2, figs. 1 e 2). Imediatamente após o PRR, todos os doentes obtiveram uma melhoria significativa na distância média da PM6m (fig. 1) e na pontuação total do SGRQ (fig. 2). No GA observou-se uma melhoria de 45,1 m na PM6m (p = 0,002) e 12,2 pontos na pontuação total do SGRQ (p = 0,002) (tabela 2, figs. 1 e 2). Os doentes do GC tiveram uma melhoria de 57,5 m na PM6m (p = 0,008) e menos 10,8 pontos na pontuação total do SGRQ (p = 0,085) (tabela 2, figs. 1 e 2). Não se verificaram diferenças estatisticamente significativas entre os grupos.

Após o PRR, no GA houve uma diminuição da distância média percorrida na PM6m aos 6 meses (−23,1 m), um ano (−32,9 m) e 2 anos (−16,0 m) (tabela 2). Contudo, estes doentes continuavam a apresentar uma distância média percorrida melhor do que antes do PRR (fig. 1) e 2 anos após

Tabela 1 Características clínicas e demográficas dos 2 grupos

	GA	GC	Valor p
Doentes	24	8	
Masculino / Feminino	20 (83,3) / 4 (16,7)	7 (87,5) / 1 (12,5)	ns
Idade (anos)	65,7 ± 10,3	70,1 ± 5,2	ns
Ex-fumadores / não fumadores	21 (87,5) / 3 (12,5)	8 (100) / 0 (0)	ns
Escala de ansiedade - depressão			ns
Ansiedade	5,5 ± 3,4	5,1 ± 4,1	
Depressão	5,0 ± 4,4	4,1 ± 2,8	
Dispneia – MRC	2,4 ± 1,1	2,3 ± 0,8	ns
Patologia pulmonar			
DPOC	13 (54,2)	5 (62,5)	ns
DPOC + sequelas TB	6 (25,0)	2 (25,0)	
Bronquiectasias	5 (20,8)	1 (12,5)	
DPOC			ns
Estádio III do GOLD	5 (26,3)	0 (0)	
Estádio IV do GOLD	14 (73,7)	7 (100)	
Provas de função respiratória			ns
Obstrução não reversível	20 (83,3)	7 (87,5)	
Alteração ventilatória mista	4 (16,7)	1 (12,5)	
VEMS previsto	42 ± 18,6	43,1 ± 13,8	
Insuficiência respiratória	18 (75,0)	8 (100)	ns
PaO_2 (mmHg)	63,3 ± 4,6	58,8 ± 4,1	0,023
Oxigenoterapia de longa duração	12 (50,0)	5 (62,5)	ns
Comorbilidades (número)	1,9 ± 0,3	3,0 ± 1,5	0,016
Doença cardiovascular			
Hipertensão arterial	6 (25)	4 (50)	
Cardiopatia isquémica	3 (12,5)	3 (37,5)	
Insuficiência cardíaca direita	3 (12,5)	1 (12,5)	
Insuficiência cardíaca congestiva	1 (4,2)	1 (12,5)	
Fibrilhação auricular	-	1 (12,5)	
Acidente vascular cerebral	1 (4,2)	1 (12,5)	
Aneurisma da aorta	1 (4,2)	1 (12,5)	
Hipertensão arterial pulmonar	1 (4,2)	-	
SAOS	2 (8,3)	5 (62,5)	
Doenças neuroendócrinas			
Diabetes mellitus	4 (16,7)	1 (12,5)	
Dislipidémia	5 (20,8)	1 (12,5)	
Outras	4 (16,7)	1 (12,5)	
Doença hepática	3 (12,5)	-	
Hipertrofia benigna da próstata	3 (12,5)	2 (25)	
Osteoporose	-	2 (25)	
Outras	5 (20,8)	2 (25)	
Índice de Charlson	1,4 ± 0,6	1,6 ± 0,8	ns
Modalidade de treino			ns (0,088)
Tapete rolante	18 (75)	3 (37,5)	
Bicicleta	6 (25)	5 (62,5)	
Duração PRR (semanas)	26,7 ± 8,7	25,5 ± 4,6	ns
Intensidade alvo atingida (%)	81,7 ± 7,1	80,0 ± 0	ns

Dados apresentados em número (%) e média ± desvio padrão.
GA: grupo ativo; GC: grupo controlo; NS: estatisticamente não significativo; MRC: *Medical Research Council*; DPOC: Doença Pulmonar Obstrutiva Crónica; TB: tuberculose; GOLD: *Global initiative for chronic Obstructive Lung Disease*; VEMS: volume expiratório máximo no 1.° segundo; PRR: programa de reabilitação respiratória; SAOS: Síndrome de Apneia Obstrutiva do Sono.

Tabela 2 Capacidade de exercício e estado de saúde

	Pré-PRR	Após o PRR			6 meses		1 ano		2 anos	
	Média	Diferença com Pré-PRR	Diferença entre grupos	Média	Diferença com após PRR	Média	Diferença com após PRR	Média	Diferença com após PRR
PM6m (m)									
GA	294,1 ± 77,4 n = 24 ±	339,2 ± 70,3 n = 24 ±	45,1 ± 62,7 p = 0,002 ±	p = 0,611	317,8 ± 94,4 n = 19 ±	−23,1 ± 64,8 p = 0,138 ±	313,1 ± 92,0 n = 16 ±	−32,9 ± 65,0 p = 0,061 ±	326,2 ± 90,3 n = 16 ±	−16,0 ± 43,4 p = 0,161 ±
GC	289,4 ± 40,4 n = 8	346,9 ± 40,4 n = 8	57,5 ± 44,2 p = 0,008		290,7 ± 67,7 n = 6	−46,8 ± 53,8	269,3 ± 71,8 n = 7	−73,6 ± 39,2 p = 0,003	255,0 ± 30,0 n = 4	−82,5 ± 15,0
SGRQ										
GA	46,6 ± 14,1 n = 24	34,4 ± 18,5 n = 24	−12,2 ± 17,6 p = 0,002	p = 0,871	–	–	40,9 ± 15,3 n = 14	8,0 ± 13,0 p = 0,038	43,2 ± 16,5 n = 17	10,1 ± 16,6 p = 0,023
GC	47,0 ± 11,6 n = 8	36,2 ± 10,6 n = 8	−10,8 ± 15,2 p = 0,085				38,5 ± 12,0 n = 2	−1,5 ± 3,5	60,3 ± 8,7 n = 3	35,43 ± 5,51

Dados apresentados em média ± desvio padrão.
GA: grupo activo; GC: grupo controlo; PRR: Programa de Reabilitação Pulmonar; PM6m: prova de marcha dos 6 minutos; SGRQ: Questionário de St George na doença respiratória.

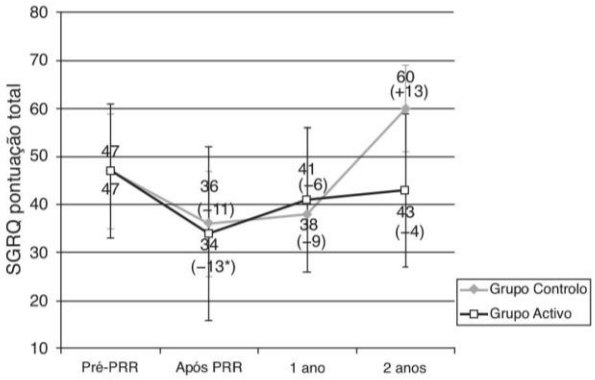

Figura 2 Resultados do questionário de St. George na doença respiratória (SGRQ). Dados apresentados em média ± desvio padrão.
PRR: programa de reabilitação respiratória. * Melhoria significativa após reabilitação (p < 0,05). Diferença (em metros) Após-Pré PRR aparece entre parêntesis.
Dimensão da amostra: 24, 24, 14, 17 para pré-PRR, após PRR, 1 ano e 2 anos, respetivamente no grupo activo; 8, 8, 2, 3 para pré-PRR, após PRR, 1 ano e 2 anos, respetivamente no grupo controlo.

o PRR, esta melhoria ainda era clínica (+32 m) e estatisticamente significativa (p = 0,034). Dois anos após o PRR, 69% dos doentes apresentavam uma distância percorrida na PM6m igual ou superior à percorrida antes do PRR.

Após completar o PRR, no GC observou-se uma tendência para um maior declínio na distância média percorrida na PM6m aos 6 meses (−46,8 m), um ano (−73,6 m) e 2 anos (−82,5 m) (tabela 2). Após 2 anos, a distância percorrida na PM6m era, em média, menos 34 metros do que antes do PRR (fig. 1).

Quando terminaram o PRR em ambos os grupos verificou-se uma melhoria do estado de saúde. No GA, um ano e 2 anos após o PRR, o SGRQ médio era de 40,9 pontos e 43,2 pontos, respetivamente, valores mais elevados do que os obtidos imediatamente após o PRR. Contudo, o estado de saúde continuava a ser melhor do que os valores obtidos antes do PRR (tabela 2 e fig. 2). Dois anos após o PRR, 65% apresentavam um resultado melhor no SGRQ, do que antes do PRR.

Pelo contrário, no GC, verificou-se uma tendência para agravamento da pontuação total do SGRQ, especialmente 2 anos após o PRR, em que o valor médio do SGRQ foi de 60,3 pontos (13,3 pontos mais do que antes do PRR) (tabela 2 e fig. 2).

Considerando a modalidade de treino, os resultados na PM6m e SGRQ a curto prazo foram semelhantes nos doentes que treinaram em tapete e bicicleta. Contudo, 2 anos após o PRR, os doentes que treinaram em cicloergómetro apresentavam um resultado pior no SGRQ (55,3 pontos), do que os doentes que treinaram em tapete rolante (40,7 pontos) (p = 0,027) (Anexo, tabela A1). Comparando com o GA (25%), no GC havia um maior número de doentes a treinar em cicloergómetro (62,5%), contudo esta diferença não era estatisticamente significativa.

Considerando como ponto de corte na duração do PRR as 26 semanas, não se observaram diferenças na PM6m e no SGRQ a curto prazo. Contudo, 2 anos após o PRR, os doentes que tiveram um treino com duração inferior a 26 semanas apresentavam um resultado pior no SGRQ, do que os doentes que tiveram um treino mais prolongado (p = 0,005) (Anexo, tabela A2).

Não se verificaram diferenças estatisticamente significativas na distância média percorrida na PM6m e na pontuação total do SGRQ relacionadas com o género e patologia pulmonar, nomeadamente no que diz respeito à presença de sequelas de tuberculose ou bronquiectasias. Também, não se observou qualquer correlação entre a idade ou o índice de Charlson e os resultados obtidos na PM6m e SGRQ (dados não apresentados).

Ao longo do estudo, 7 doentes do GA (26%) e 4 do GC (50%) faltaram às consultas de *follow up* (figs. 1 e 2). As características clínicas e demográficas basais foram similares nos doentes que completaram o *follow up* e nos que saíram do estudo (*drop out*) (Anexo, tabela A3).

Discussão

Os benefícios do PRR em doentes com patologia respiratória crónica são já conhecidos, estão bem documentados[1–5], e foram igualmente observados neste estudo. Em ambos os grupos, após o PRR, os doentes apresentaram uma melhoria clínica e estatisticamente significativa no estado de saúde e na capacidade funcional.

No nosso estudo todos os doentes atingiram a intensidade alvo de 80% da potência de pico, situação distinta da reportada por Maltais et al.[20], onde apenas 11,9% dos doentes com DPOC moderada e grave atingiram a intensidade alvo, após 12 semanas de treino. Todos os nossos doentes atingiram a intensidade alvo, porque a duração do treino foi ajustada de forma a alcançar este objetivo. Um treino de elevada intensidade permite atingir uma adaptação fisiológica mais pronunciada (menores necessidades ventilatórias, diminuição da acidose láctica e melhoria na tolerância ao exercício), tal como foi demonstrado por Casaburi et al.[21].

Tanto quanto é do nosso conhecimento, este é o primeiro estudo onde a maioria dos doentes com DPOC grave e muito grave mantêm a melhoria na distância percorrida na PM6m e no estado de saúde, 2 anos após o PRR, quando comparado com os valores pré-PRR.

No nosso estudo a duração e localização do programa podem ter influenciado os bons resultados obtidos após o programa de reabilitação e a adesão do GA. A duração do nosso PRR é maior do que o habitual (cerca de 26 semanas), devido à gravidade e idade avançada dos doentes. Outros estudos constataram que programas mais longos parecem potenciar os efeitos a longo prazo[2,22]. Na nossa opinião, PRR mais longos, com um contacto próximo dos doentes e seus cuidadores com a equipa multidisciplinar, em contexto de hospital de dia, favorecem os bons resultados da reabilitação.

Heppner et al.[23] também constataram que a prática de exercício regular após conclusão da reabilitação pulmonar está associada a um declínio mais lento no estado de saúde global e na capacidade de realizar caminhadas, bem como menor progressão da dispneia durante as atividades diárias. Contudo, neste estudo os doentes DPOC eram menos graves (moderados a graves).

Num estudo prévio, Spencer et al. demonstraram que a realização de treino de exercício supervisionado semanalmente em ambulatório era capaz de manter a capacidade funcional e o estado de saúde dos doentes durante 12 meses[7]. Nesse estudo, o grupo controlo, que realizava exercício não supervisionado em casa também manteve esses benefícios. O grupo controlo deste estudo era semelhante ao nosso GA e os resultados a longo prazo foram similares, contudo os doentes do nosso estudo eram mais graves (Spencer et al. estudaram doentes com DPOC moderada)[7] e mantiveram estes benefícios durante 2 anos.

Noutro estudo, Brooks et al.[9] compararam os efeitos de 2 programas pós-reabilitação ao nível da capacidade funcional e do estado de saúde em doentes com DPOC grave. Num grupo, os doentes eram observados em sessões mensais de grupo e recebiam um telefonema quinzenal da fisioterapeuta; no outro grupo, os doentes visitavam a fisioterapeuta a cada 3 meses. Tal como no nosso estudo observou-se, após o programa de reabilitação, uma melhoria significativa na PM6m e no SGRQ. Contudo, neste estudo houve uma deterioração franca na capacidade funcional e no estado de saúde, 12 meses após o término da reabilitação respiratória, em ambos os grupos.

A baixa adesão à prática de exercício regular tem um efeito prejudicial na morbilidade, mortalidade e recurso a cuidados de saúde[9]. Não temos uma explicação para a fraca adesão do GC a um estilo de vida ativo, uma vez que ambos os grupos apresentavam características clínicas e demográficas semelhantes e benefícios de magnitude similar com o PRR (tabela 1). A transferência das competências adquiridas pelo doente para o seu estilo de vida habitual pode ser dificultada por diversos obstáculos: falta de autoconfiança, alterações cognitivas, problemas comportamentais, baixa motivação e presença de barreiras físicas no domicílio ou na comunidade[24,25]. No nosso estudo, o Grupo Controlo, sendo menos aderente ao exercício, apresentou igualmente uma menor adesão às consultas de *follow-up*.

Os doentes que treinaram em bicicleta obtiveram, a longo prazo, piores resultados na capacidade funcional e no estado de saúde. Uma possível explicação poderá ter sido a dificuldade em manter esta modalidade de forma regular no domicílio e consequentemente, os doentes tornaram-se mais inativos.

Apesar da PaO_2 média ser inferior no GC (p = 0,023), o que poderia representar uma condição limitante, não havia diferença estatisticamente significativa no número de doentes em oxigenoterapia de longa duração (tabela 1). O GC apresentava um maior número de comorbilidades (3 *versus* 1,9, p = 0,016), contudo o índice de Charlson era similar em ambos os grupos.

A idade, o género e a presença de sequelas de tuberculose ou as bronquiectasias também não tiveram aparente influência nos resultados.

Na nossa opinião a fraca adesão ao exercício pode ter causado deterioração da condição de saúde dos doentes do GC, com consequente redução da capacidade funcional e estado de saúde.

As limitações deste estudo incluem a pequena dimensão da amostra, com maior redução devido aos doentes que

abandonaram o *follow-up* e o facto de se tratar de um estudo retrospetivo.

Apesar do auto-relato da atividade física ser um possível viés (uma vez que não conseguíamos confirmar os níveis de atividade física dos doentes), os resultados mostraram concordância, com maiores benefícios no grupo que afirmava manter exercício regular.

Os resultados deste estudo apontam para a necessidade de maior investigação nesta área, de forma a identificar características prognósticas relacionadas com sucesso / insucesso a longo prazo da reabilitação respiratória e o desenvolvimento de estratégias para manter os benefícios da reabilitação.

Conclusão

Um programa de reabilitação respiratória com cerca de 26 semanas de duração, num hospital de dia de insuficientes respiratórios, em doentes com doença pulmonar crónica grave e muito grave conduz a benefícios significativos na capacidade funcional e no estado de saúde. Esses benefícios diminuem após término do programa, mas mantêm-se significativamente positivos 2 anos após sua conclusão, em doentes motivados e aderentes à prática de exercício.

A prática de exercício regular após um programa de reabilitação parece ser um fator protetor contra a perda de capacidade funcional e do estado de saúde em doentes com doença pulmonar crónica grave e muito grave.

Apesar de a amostra ser pequena, este estudo comprova a necessidade de implementar estratégias que assegurem a manutenção dos benefícios da Reabilitação Respiratória.

Conflito de interesses

Os autores declaram não haver conflito de interesses.

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Anexo.

Tabela A1.
Tabela A2.
Tabela A3.

Tabela A1 Modalidade de treino e resultados na PM6m e SGRQ

	n	Bicicleta	n	Tapete	Valor p
PM6m					
Antes do PRR	11	300,5 ± 60,8	21	288,9 ± 74,8	ns
Imediatamente após o PRR	11	351,9 ± 58,2	21	335,5 ± 67	ns
2 anos após o PRR	6	275 ± 51,7	14	327,9 ± 94,5	ns
SGRQ					
Antes do PRR	11	41,8 ± 13,7	21	49,2 ± 12,8	ns
Imediatamente após o PRR	11	31,3 ± 14,9	21	36,8 ± 17,7	ns
2 anos após o PRR	7	55,3 ± 17,8	13	40,7 ± 14,1	0,027

SGRQ: questionário de St. George na doença respiratória; PM6m: prova de marcha dos 6 minutos; PRR: programa de reabilitação respiratória; NS: estatisticamente não significativo.

Tabela A2 Duração do treino e resultados na PM6m e SGRQ

	n	Treino < 26 semanas	n	Treino ≥ 26 semanas	Valor p
PM6m					
Antes do PRR	17	304,5 ± 78,5	15	279,8 ± 57,4	ns
Imediatamente após o PRR	17	354,5 ± 51,5	15	326 ± 74	ns
2 anos após o PRR	13	299,6 ± 73,1	7	335 ± 109	ns
SGRQ					
Antes do PRR	17	52,2 ± 9,7	15	40,4 ± 14,4	0,01
Imediatamente após o PRR	17	35,9 ± 15,3	15	33,7 ± 18,7	ns
2 anos após o PRR	13	53 ± 11,9	7	32,4 ± 16,5	0,005

SGRQ: questionário de St. George na doença respiratória; PM6m: prova de marcha dos 6 minutos; PRR: programa de reabilitação respiratória; NS: estatisticamente não significativo.

Tabela A3 Características basais dos doentes que completaram o *follow-up* e dos doentes que abandonaram (*drop out*)

	Drop out	Follow up	Valor p
Doentes	11	21	
Masculino / Feminino	9 (81,8) / 2 (18,2)	18 (85,7) / 3 (14,3)	ns
Idade (anos)	68 ± 9,8	66,2 ± 4,6	ns
Ex-fumadores / não fumadores	10 (90,9) / 1 (9,1)	19 (90,5) / 2 (9,5)	ns
Escala de ansiedade - depressão			ns
Ansiedade	5,9 ± 3,5	5,2 ± 3,6	
Depressão	4,6 ± 4,0	5,2 ± 3,6	
Dispneia – MRC	2,4 ± 1,0	2,4 ± 1,0	ns
Patologia pulmonar			
DPOC	6 (54,5)	12 (57,1)	ns
DPOC + sequelas TB	3 (27,3)	5 (23,8)	
Bronquiectasias	2 (18,2)	4 (19,1)	
DPOC			ns
Estádio III do GOLD	0	5 (29,4)	
Estádio IV do GOLD	9 (100)	12 (70,6)	
Provas de função pulmonar			ns
Obstrução não reversível	9 (81,8)	18 (85,7)	
Alteração ventilatória mista	2 (18,2)	3 (14,3)	
VEMS previsto	47,5 ± 23,5	39,6 ± 12,8	
Insuficiência respiratória	11 (100)	15 (71,4)	ns
PaO_2 (mmHg)	61,8 ± 5,3	62 ± 4,6	ns
Oxigenoterapia de longa duração	8 (72,7)	9 (42,8)	ns
Índice de Charlson	1,4 ± 0,5	1,7 ± 0,9	ns
Duração do PRR (semanas)	28,1 ± 10,5	25,5 ± 6,1	ns
Modalidade de Treino			ns
Bicicleta	4 (36,4)	7 (33,3)	
Tapete	7 (63,6)	14 (66,7)	
Intensidade alvo atingida (%)	80,9 ± 8,4	81,5 ± 4,9	ns
PM6m			ns
Antes do PRR	303,4 ± 36,6	287,4 ± 82	
Imediatamente após o PRR	330,9 ± 61,7	346,5 ± 65,5	

Dados apresentados em número (%) e média ± desvio padrão.
NS: estatisticamente não significativo; MRC: *Medical Research Council*; DPOC: Doença Pulmonar Obstrutiva Crónica; TB: tuberculose; GOLD: *Global initiative for chronic Obstructive Lung Disease*; FEV_1: volume expiratório máximo no 1.° segundo; PRR: programa de reabilitação respiratória; PM6m: prova de marcha dos 6 minutos.

Bibliografia

1. Casaburi R, ZuWallack R. Pulmonary Rehabilitation for Management of Chronic Obstructive Pumonary Disease. N Engl J Med. 2009;360:1329–35.
2. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease (Review). The Cochrane Library. 2009;3:1–56.
3. Pamplona P, Morais L. Treino de exercício na doença pulmonar crónica. Rev Port Pneumol. 2007;XIII:101–28.
4. Ries A, Bauldoff G, Carlin B, Casaburi R, Emery C, Mahler D, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical practice Guidelines. Chest. 2007;131:4–42.
5. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American Thoracic Society /European Respiratory Society Statement on Pulmonary Rehabilitation. Am J Resp Crit Care Med. 2006;173:1390–413.
6. Chairman M, Calverley P, Clark C, Davidson A, Garrod R, Goldman J, et al. BTS statement: Pulmonary rehabilitation. Thorax. 2001;56:827–34.
7. Spencer L, Alison J, McKeough Z. Maintaining benefits following pulmonary rehabilitation: a randomised controlled trial. Eur Resp J. 2010;35:571–7.
8. Riera S, Rubio T, Ruiz F, Ramos P, Otero D, Hernandez T, et al. Inspiratory muscle training in patients with COPD: effect on dyspnoea, exercise performance and quality of life. Chest. 2001;120:748–56.
9. Brooks D, Krip B, Mangovski-Alzamora, Goldstein R. The effect of postrehabilitation programmes among individuals with chronic obstructive pulmonary disease. Eur Resp J. 2002;20:20–9.
10. Wewel A, Gellerman I, Schwertfeger I, Morfeld M, Magnussen H, Jorres R. Intervention by phone calls raises domiciliary activity and exercise capacity in patients with severe COPD. Resp Med. 2008;102:20–6.

11. Charlson M, Sztrowski T, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47:1245–51.
12. Hall W, Ramachandran R, Narayan S, Jani A, Vijayakumar S. An electronic application for rapidly calculating Charlson comorbidity score. BMC Cancer. 2004;4:94.
13. Incalzi R, Fuso L, Rosa M, Forastiere F, Rapiti E, Nardecchia B, Pistelli R. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. Eur Resp J. 1997;10:2794–800.
14. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52:69–77.
15. Bestall J, Paul E, Garrod R, Garnham R, Jones P, Wedzicha J. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54:581–6.
16. ATS statement: guidelines for the six-minute walk test. Am J Crit Care Med. 2002;166:111–7.
17. Jones P, Quirk F, Baveystock C. The St George's Respiratory Questionnaire. Respir Med. 1991;85:25–31.
18. Holland A, Hill C, Rasekaba T, Lee A, Naughton M, McDonald F. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil. 2010;91:221–6.
19. Jones P. St. George's Respiratory Questionnaire: MCID. COPD. 2005;2:75–9.
20. Maltais F, LeBlanc P, Jobin J, Berube C, Bruneau J, Carrier L, et al. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;2:555–61.
21. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis. 1991;143:9–18.
22. Troosters T, Gosselink R, Decramer M. Short and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease:a randomized trial. Am J Med. 2000;109:207–12.
23. Heppner P, Morgan C, Kaplan R, Ries A. Regular walking and long-term maintenance of outcomes after pulmonary rehabilitation. J Cardiopulm Rehabil. 2006;26:44–53.
24. Ferri M, Brooks D, Goldstein RS. Do our patients do what we ask of them? The what, why and how of compliance to treatment. Physiother Can. 1998;50:286–90.
25. Fischer M, Abbink J, Nies A, Rudolphus A, Weinman J, Kaptein A. Participation and drop-out in pulmonary rehabilitation: a qualitative analysis of the patient's perspective. Clinical Rehabilitation. 2007;21:212–21.

Original Research

TELEMOLD Project: Oximetry and Exercise Telemonitoring to Improve Long-Term Oxygen Therapy

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Abstract

Background: *Standard assessment of long-term oxygen therapy (LTOT) prescription involves hospital-based clinical tests. However, there is some evidence suggesting that oxygen demand during daily activities may not be correctly estimated by such tests, when compared with continuous ambulatory oximetry. The authors describe the results of a study aiming to evaluate the clinical relevance of a home telemonitoring system in LTOT optimization.* ***Subjects and Methods:*** *Thirty-five chronic respiratory failure patients were monitored in real time with an oximeter sensor and an accelerometer. Signals were sent via Bluetooth® (Bluetooth SIG, Kirkland, WA) to a mobile phone and then via 3G or general packet radio service to a server. Continuous and secure access to data was established through an Internet site.* ***Results:*** *Each patient was monitored an average of 7.6±4.5 days (total, 83±67 h). Valid records were on average 65±24%. Records of rest, activity, and sleep time per patient were, on average, 28±21%, 7±6%, and 59±25%, respectively. Significant desaturation during rest, activity, and sleep was found in 2, 26, and 9 patients, respectively. Patients' ratings of the user-friendliness of the equipments, assessed by questionnaire, were fairly good (76% reported it as easy/very easy).* ***Conclusions:*** *Our study suggests that a telemonitoring system combining oximetry and physical activity evaluation might contribute to a more adequate oxygen prescription, mainly during daily activities.*

Key words: *accelerometry, chronic obstructive pulmonary disease, physical activity, rehabilitation, respiratory failure, telemedicine*

Introduction

New communication technologies have a prime and expanding relevance to healthcare development. Telemedicine is a fine example of integrating these technologies into medical practice. In respiratory medicine, applications of telemedicine have been described in the fields of home-based diagnosis and monitoring, of data interpretation at specialized centers, and of centralized pulmonary function measurement in clinical trials.[1–3]

In this study, we describe the use of a telemedicine technology, in an ambulatory setting, that combines real-time monitoring with an oximeter sensor and with an accelerometer. This combined use can potentially improve long-term oxygen therapy (LTOT).

Currently, the standard assessment to prescribe LTOT involves periodic clinical examinations (arterial blood gas measurement, the 6-min walk test [6MWT], and nocturnal oximetry) carried out over several hospital visits. However, there is some evidence that oxygen demand during daily activities may not be correctly estimated by such tests when compared with the evaluation carried out with continuous ambulatory oximetry.[4,5]

Simultaneous and remote monitoring of oxygen levels and physical activity through the use of an oximeter sensor and an accelerometer might allow a better adequacy of oxygen needs according to different levels of physical activity, allowing chronic respiratory failure patients to perform their daily living activities with the appropriate level of oxygen saturation (SpO_2).

Inactivity is a hallmark manifestation in chronic respiratory failure patients, well studied in chronic obstructive pulmonary disease (COPD), and has been proved to be a negative influence on prognosis. The acknowledgment of physical activity as the strongest predictor of all-cause mortality in COPD patients brings increasing interest to exercise quantification in daily life.[6,7] Traditionally, this parameter has been estimated from questionnaires and clinical interviews, but the recent introduction of accelerometers enables a more accurate evaluation of daily exercise.[7–9] The American College and Sports Medicine and the American Heart Association recommend that 30 min of moderate intense physical activities on at least 5 days per week is needed to yield health benefits.[10] Moderate intensity is usually considered for healthy adults as 3.0–6.0 metabolic equivalents of task (METs).[11]

The aim of the present study was to evaluate the clinical value of telemonitoring with oximetry and an accelerometer, assessed in terms of its capacity to detect oxygen desaturation occurring in real-life situations and its potential contribution to improving LTOT prescription, as well as to monitor physical activity. Patients' acceptance of and difficulties on using the devices were also evaluated.

Subjects and Methods

The TELEMOLD project included three phases. The first phase consisted of the development of the software required for the

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simultaneous monitoring of patients' oxygen levels and physical activity. A mobile application was developed for data exchange between monitoring equipment and a central database. The equipment characteristics and design took into account its autonomy, ease of handling, and low interference in daily activities. In the second phase, TELEMOLD was tested by volunteer healthy subjects to assure its correct functioning concerning the oximeter and the accelerometer in different exercise modalities. Finally, in the third phase, the system was applied in our patient population. This article reports the results of the project's third phase.

SUBJECTS

From the group of chronic respiratory failure patients followed up in our Pulmonary Rehabilitation Unit, we consecutively selected a sample of 35 patients, independently of already being under LTOT or not, as evaluated by conventional methods. All patients underwent a 6MWT, arterial blood gas measurement, and nocturnal oximetry, and oxygen prescription was optimized. All patients were clinically stable, receiving optimal pharmacological treatment, and under pulmonary rehabilitation program. All patients were encouraged to follow an active lifestyle, given information about the importance of exercise, and taught the type and intensity of exercise they can do according to what they perform in rehabilitation sessions. Exclusion criteria were a patient's illiteracy or cognitive deficit and absence of a caregiver. The Ethics Committee of the Centro Hospitalar de Lisboa Norte approved the study protocol, and subjects gave written informed consent.

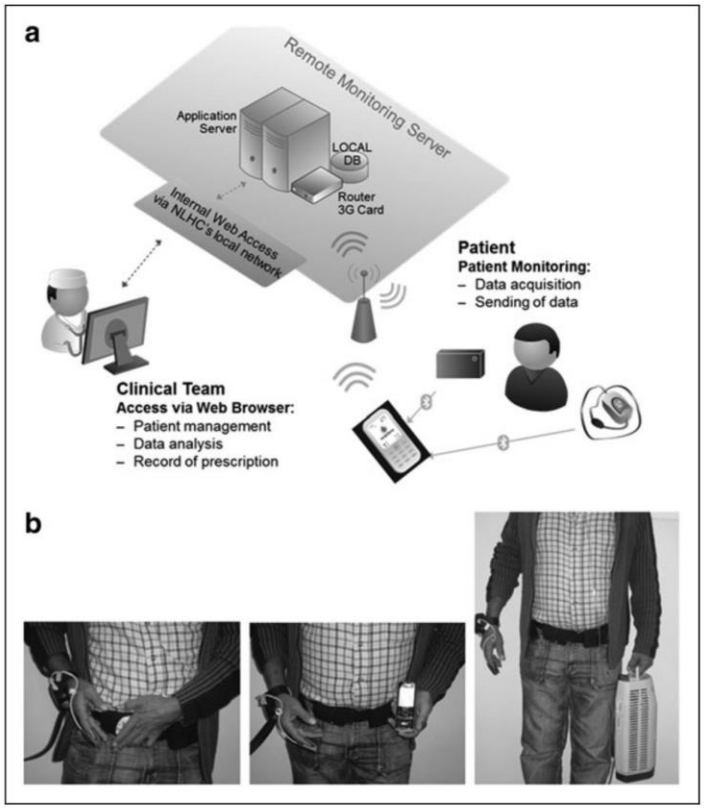

Fig. 1. (a) TELEMOLD functioning scheme and **(b)** patient monitored with a oximeter sensor, accelerometer, and mobile phone. DB, database; NLHC, North Lisbon Hospital Center.

STUDY DESIGN

Patients were connected to a digital oximeter sensor (Avant 4000™; Nonin Medical, Plymouth, MN) portable module for acquisition of transcutaneous SpO_2 and heart rate and an accelerometer (bioPlux Motion™; Biosensor Engineering, Lisbon, Portugal)[12] that allowed the acquisition of MET related to the patient's activity level. The collected signals were sent via Bluetooth® (Bluetooth SIG, Kirkland, WA) to a mobile phone that processed and sent them, via 3G or general packet radio service, to a server. The data were saved in a server database located at the Centro Hospitalar de Lisboa Norte with restricted, password-secured personal access.

Access via a Web browser allowed continuous and real-time viewing of the collected data. Relevant clinical information like diagnosis and oxygen prescription details was added to each patient's file (*Fig. 1*).

The equipment was delivered to the patients, and instructions were given in individual sessions of about 20–30 min. Patients were asked to use TELEMOLD at different times of the day, according to the equipment's battery autonomy (accelerometer, 24 h; oximeter, 1–2 days; mobile phone, 4–6 h) and to each patient's daily routine. Periods of rest, exercise, and sleep should be covered by all subjects. They were also asked to fill in a record sheet, where all their activities throughout the monitoring period were recorded. One week of monitoring was suggested, although in some cases this period could be modified for the patient's convenience. At the end, subjects were invited to answer a questionnaire reporting the difficulties they experienced.

The recorded data were evaluated daily by the clinical staff, through the analysis of the Web interface graphics (*Fig. 2*). Whenever a problem was identified, the subject, or a caregiver, was contacted by phone.

DATA ANALYSIS

The following definitions were used:

- Exercise was defined as any activity ≥2.5 METs for at least 3 consecutive min together with ≥20% increase in the basal heart rate. Sleep was recognized through the patient's report. Rest was defined by exclusion.
- Records were considered valid if they included ≥4 h of oximeter monitoring in sleep, ≥30 min of oximeter and accelerometer monitoring in rest, and ≥3 min also with both devices in exercise.

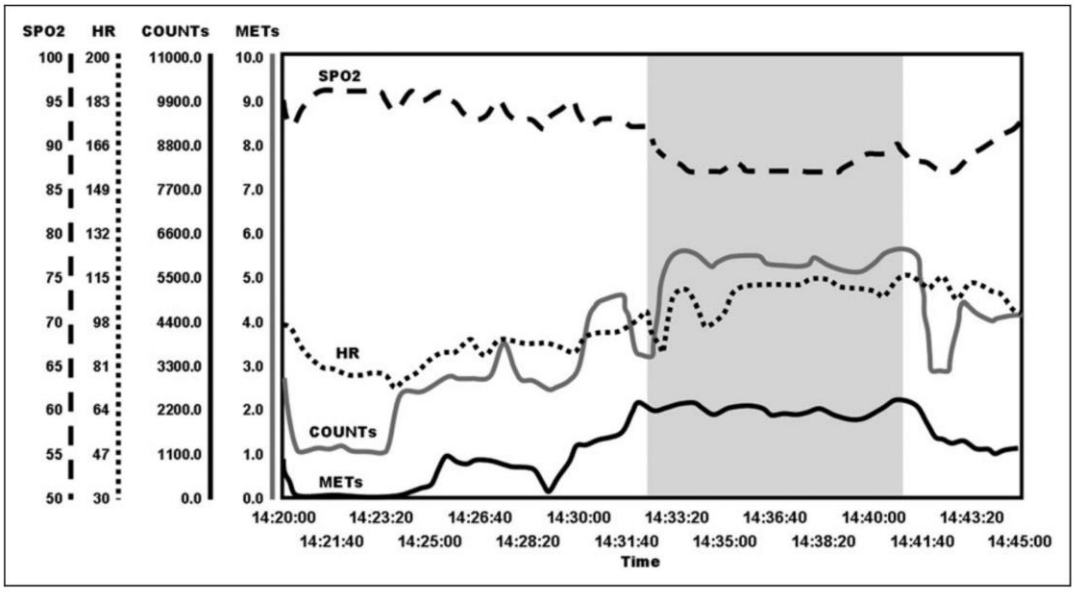

Fig. 2. TELEMOLD collected data. The shadowed area highlights the period where a rise of metabolic equivalent of task (MET) scores occurs simultaneously with the drop of oxygen saturation (SpO_2). HR, heart rate.

- Significant oxygen desaturation was defined as SpO_2 <90% in ≥30% of the sleep time recorded, at least in 1 night,[13,14] SpO_2 <88% in ≥30% of the resting time,[5,15–17] or SpO_2 <88% in at least two recordings of 3 min each in exercise.[5,18]

Only valid records were analyzed for oxygen desaturation.

Descriptive statistics were carried out for the variables considered. Data analysis was performed using SPSS (Statistical Package for Social Sciences) version 18 software (SPSS, Inc., Chicago, IL).

Results

Among the 39 patients initially selected, 4 refused to participate, stating that the system was too complex. The clinical and epidemiological characteristics of the 35 participants are described in *Table 1*. COPD was the most prevalent diagnosis (63%; $n=22$), followed by interstitial lung disease (17%; $n=6$). All patients had hypoxemia, and 18 subjects also had hypercapnia; 29 were under LTOT. Ten patients were also under nocturnal noninvasive mechanical ventilation.

Data recorded by the system are given in *Table 2*. The mean number of hours recorded per patient was 83.0 ± 66.9 h. The subjects used the devices for 7.6 ± 4.5 days, on average, corresponding to a mean of 10.5 ± 4.7 h/day. The percentage of valid records per patient was 65 ± 24%, ranging from a total lack of valid data ($n=2$) to 100% ($n=1$) (*Fig. 2*). The proportion of rest, exercise, and sleep records was, on average, 28 ± 21%, 7 ± 6%, and 59 ± 25% of valid recorded time, respectively (*Fig. 3*).

Significant desaturation was found in 2 patients during rest (6,5%), in 26 patients during exercise (87%), and in 9 patients during sleep (27%). In these 9 patients, oxygen desaturation occurred in 69% of all recorded nights.

Seven of the 35 patients (20%) filled in the record sheet describing the different activities performed during each day of monitoring. The activities reported by patients were related to the movement during daily life activities like dressing, going shopping, going down the stairs of the building, and, in some cases, outdoor trips.

Thirty-three patients answered the questionnaire evaluating TELEMOLD user-friendliness; of these, 76% ($n=25$) reported its use as "very easy"/"easy" (*Table 3*). Recharging the devices' batteries was difficult for 33% ($n=11$) of the patients.

Discussion

To our knowledge, this is the first report of a telemonitoring system combining the use of continuous oximetry and physical activity quantification through an accelerometer, in monitoring chronic respiratory failure patients. We found significant oxygen desaturation occurring in all defined periods, but exercise desaturation was by far the most relevant.

Although no comparison with conventional tests was performed in our study, these findings suggest that conventional tests may underestimate desaturation occurring in real-life situations.

Concerning rest periods, we found only 2 patients with desaturation >30% of the time. These results suggest that arterial blood gas correctly estimates oxygen needs at rest in the majority of patients.

On the other hand, 87% of our patients had important desaturation occurring during activity, which may suggest that the oxygen demand in exercise evaluated by a timed walking test may underestimate the real needs in daily life activities. Although 6MWT has been shown to be a reliable measurement, namely, when compared with ambulatory pulse oximetry as performed by Morante et al.,[19] several

Table 1. Clinical and Epidemiological Characteristics of Patients ($n=35$)

CHARACTERISTIC	VALUE
Gender	
Male	28 (80)
Female	7 (20)
Average age (years)	64.7 ± 10.8
Race	
White	34 (97.1)
Black	1 (2.9)
School attending (years)[a]	7.0 ± 4.1
Diagnosis	
COPD	22 (62.9)
Interstitial lung disease	6 (17.1)
Asthma	3 (8.6)
Tuberculosis sequelae	3 (8.6)
Chest wall disease	1 (2.9)
Tobacco usage	
Ex-smokers	20 (57.1)
Smokers	7 (20)
Tobacco load (packs per year)	48.5 ± 36.1
BMI $\geq 30\ kg/m^2$	12 (34.3)
Comorbidities (n)	2.3 ± 1.6
Lung function pattern[b]	
Obstructive	27 (81.8)
Post-BD FEV_1	39.9 ± 21.2% (17–114)[c]
Restrictive	2 (6.1)
FVC	55 ± 11.3% (47–63)[c]
Mixed	2 (6.1)
FVC	58.5 ± 0.7% (58–59)[c]
FEV_1	45 ± 19.8% (31–59)[c]
Decreased DLCO	1 (3)
Respiratory failure	
Hypoxemic	17 (48.6)
Hypercapnic	18 (51.4)
Patients on LTOT	29 (82.9)
Patients under NIMV	10 (28.6)

Data are *n* (%) or mean ± standard deviation values.

[a]Data available for 33 patients.

[b]Data available for 32 patients (data from 3 patients were not considered for analysis because of deficient cooperation).

[c]Numbers in parentheses are minimum–maximum.

BD FEV_1, forced expiratory volume in 1 s after bronchodilator; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DLCO, diffusing lung capacity for carbon monoxide; FVC, forced vital capacity; LTOT, long-term oxygen therapy; NIMV, noninvasive mechanical ventilation.

Table 2. Recorded Data per Patient According to the Individual's Activity Levels

	MEAN±SD	MINIMUM	MAXIMUM
Total hours	83.0 ± 66.9	4.8	228.8
Total days	7.6 ± 4.5	2	19
Hours per day	10.5 ± 4.7	0.6	20.2
Valid hours			
n	60.3 ± 56.5	0	183.8
%[a]	65.4 ± 24.1	0	100
Rest (h)			
n	18.6 ± 20.2	0	79.7
%[b]	28.4 ± 21.3	0	97.8
Activity (h)			
n	4.4 ± 5.5	0	26.9
%[b]	6.5 ± 5.5	0	19.7
Sleep (h)			
n	37.2 ± 36.6	0	147.5
%[b]	59.3 ± 24.6	0	100

[a]Percentage per number of total hours of recorded data.

[b]Percentages per number of valid hours of recorded data.

SD, standard deviation.

disadvantages of its use have been pointed. Guyatt et al.[20] showed the dependence on patient and administrator motivation, the learning effect, and intertest variability. Additionally, these tests only access the patient at one point in time in a controlled laboratory setting, and they evaluate level-ground walking, which is not indicative of, and often underestimates, ambulatory tasks in real-life situations.

Concerning oxygen prescription during sleep, there are no consensual recommendations; there are three ways to adjust oxygen flow rate: maintaining the resting flow, increasing it in 1 or 2 L/min, or setting the flow rate according to continuous monitoring of SpO_2.[14,21,22] In this study we considered more than 30% of nighttime with SpO_2 <90% (at least in 1 night) as abnormal, and we found it in 27% of the patients. However, in this particular group of patients, desaturation was not detected in every recorded night. We hypothesize that nocturnal oximetry performed in a single night may be insufficient to detect important sleep desaturation in some patients, as also suggested by Lewis et al.[23]

Previous studies also suggest that standard evaluation of everyday life need for oxygen therapy may be inadequate. Schenkel et al.[24] used continuous oximetry to study 30 COPD patients with no resting hypoxemia and showed transient oxygen desaturation, with mean SpO_2 being lower during the night than during the day, but with the lowest recorded SpO_2 occurring during daytime activities. Sliwiński et al.[25] used continuous oximetry in 34 patients under LTOT and

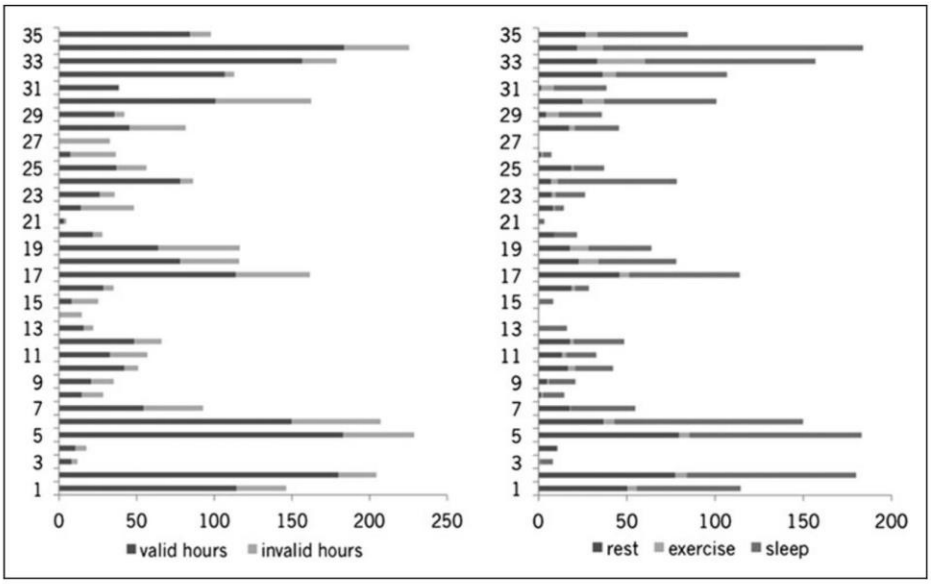

Fig. 3. (Left panel) Valid and invalid records per patient and **(right panel)** distribution of the valid records per periods of rest, exercise, and sleep (in h).

found a mean SpO_2 of 94% at rest but 29% of monitored time with SpO_2 under 90%. In a study developed by Pilling and Cutaia,[26] 20 of 27 patients with stable COPD spent more than 10% of the monitored time with SpO_2 under 90%. More recently, Fussell et al.[5] compared resting oxygen desaturation and 6MWT versus continuous ambulatory oximetry in a group of 20 COPD patients who were being evaluated for LTOT and found poor correlation between these two methods.

In the studies from Schenkel et al.[24] and Sliwiński et al.,[25] exercise was only assessed by questionnaires, a method that is highly dependent on patients' collaboration and memory. In our study, for instance, only 7 (20%) patients filled in the record sheet. On the other hand, simultaneous and continuous monitoring and recording of both SpO_2 and activity, as performed in our study, allowed us to confidently correlate the occurrence of exercise desaturation with its intensity.

Some technical aspects of the study deserve consideration. Each patient had to carry three different devices, and several buttons had to be turned on/off. Additionally, each one of them had to be charged at different times of the day. Those facts, combined with the low literacy of this group of patients (7 years, on average), probably explains the 36% of invalid data obtained. In fact, 33% of patients reported problems with charging the batteries, and although only 6 patients (18%) described TELEMOLD use as "difficult," the clinical staff felt that a larger number faced difficulties in understanding the system's functioning, requiring further phone calls for clarifications. The strategy of asking patients to track moments of their everyday life was fundamental in providing us with valid data from all three periods (rest, exercise, and sleep). The emerging smartphone technology can be the answer to those limitations, while allowing the incorporation of an accelerometer in the mobile phone.

The most noticeable limitation of our study is the impossibility to assure that the patients were complying with oxygen prescription in terms of number of hours and flow rates, which could have compromised the results, despite their report of good compliance. The future development of methods that allow long-term monitoring of actual oxygen usage by subjects will improve the value of trials of LTOT like the one here described.[27] Also, the fact that patients with sleep apnea were not excluded (even if they were under optimized noninvasive mechanical ventilation or LTOT) may have influenced sleep desaturation results.

The authors believe that a system like TELEMOLD, while allowing remote and real-time access to data, provides healthcare professionals with a promising tool for more appropriate monitoring of chronic respiratory patients. Also, because it combines oximetry with physical activity quantification, it can lead us to a new way of prescribing oxygen supplementation according to different levels

Table 3. Patients' Opinions on TELEMOLD Use

OPINION	*N* (%)
In your opinion, TELEMOLD utilization was…?	
Very easy	5 (15.2)
Easy	20 (60.6)
Uncomfortable	2 (6.1)
Daunting	0 (0.0)
Difficult	6 (18.2)
Was it difficult to charge the devices?	
Yes	11 (33.3)
What was the main problem with TELEMOLD use?	
None	15 (45.5)
Device's battery short life/coordinating charge of different devices	7 (21.2)
Limitation of daily life activities	4 (12.1)
Too much information on adaptation	2 (6.1)
Low signal	1 (3.0)
Other	4 (12.1)

of physical activity. The importance of an optimal timing and dosage of oxygen supplementation through a detailed and individualized activity-dependent prescription has also been pointed out by the National Heart, Lung, and Blood Institute Workshop report as one of the priority topics for future research in LTOT.[27] However, further investigation is still needed to prove that an activity-dependent oxygen prescription offers real benefit compared with the traditional methods, and this would require a randomized large-scale study.

TELEMOLD may also be used to detect patients with no indication for LTOT, which can be cost-saving. Other benefits are foreseen, such as allowing simultaneous monitoring of a large number of patients, reducing the number of hospitalizations, and reducing the number of hospital visits.[28] Hospital visits could be reduced thanks to the possibility of detecting desaturation, changing oxygen flow rates, and confirming the success of these changes within the same monitoring period. Additionally, because TELEMOLD uses Web technology, it allows the exchange of information between healthcare providers. In theory, it could be associated with an important economic benefit, as has been demonstrated in previous studies of home telehealth in chronic disease management.[29] However, this must be confirmed through a cost-effectiveness analysis.

Finally, the authors believe this technology has the potential to enhance compliance with exercise regimens aside from a supervised setting, which could yet be another direction for future investigation.

Conclusions

A telemonitoring system combining oximetry and physical activity quantification is applicable to clinical practice and might contribute to a more adequate oxygen prescription, mainly during activities of daily living. Telemedicine in chronic respiratory disease management is a promising technology, and further investigation in this area should be encouraged.

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REFERENCES

1. Cooper CB. Respiratory applications of telemedicine. *Thorax* **2009;**64:189–191.
2. Zamith M, Gomes MJM. Novas tecnologias da informação em pneumologia. *Rev Portuguesa Pneumol* **2005;**XI(Suppl 1):S21–S28.
3. Zamith M, Cardoso T, Matias I, et al. Telemonitorização domiciliária de insuficientes respiratórios crónicos graves e de doentes asmáticos. *Rev Portuguesa Pneumol* **2009;**XV:385–417.
4. Casanova C, Hernández C, Sánchez A, et al. Twenty-four hour ambulatory oximetry monitoring in COPD patients with moderate hypoxemia. *Respir Care* **2006;**51:1416–1423.
5. Fussell KM, Ayo DS, Branca P, et al. Assessing need for long-term oxygen therapy: A comparison of conventional evaluation and measures of ambulatory oximetry monitoring. *Respir Care* **2003;**48:115–119.
6. Waschki B, Kirsten A, Holz O, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPD. *Chest* **2011;**140:331–342.
7. Pitta F, Troosters T, Spruit MA, et al. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **2005;**171:972–977.
8. Agusti A. Physical activity and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **2008;**177:675–679.
9. Steele BG, Holt L, Belza B, et al. Quantitating physical activity in COPD using a triaxial accelerometer. *Chest* **2000;**117:1359–1367.
10. Haskell WL, Lee I-M, Pate RR, et al. Physical activity and public health: Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc* **2007;**39:1423–1434.
11. Nelson NE, et al. Physical activity and public health in older adults: Recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation* **2007;**116:1094–1105.
12. Silva H, Palma SP, Gamboa H, et al. AAL+: Continuous institutional and home care through wireless biosignal monitoring systems. In: Bos L, Dumay A, Goldschmidt L, Verhenneman G, Yogesan K, eds. *Handbook of Digital Homecare, Vol. 3*, 2nd ed. New York: Springer, **2011:**115–142.
13. Levi-Valensi P, Weitzenblum E, Rida Z, et al. Sleep-related oxygen desaturation and daytime pulmonary haemodynamics in COPD patients. *Eur Respir J* **1992;**5:301–307.
14. Nisbet M, Eaton T, Lewis C, et al. Overnight prescription of oxygen in long term oxygen therapy: Time to reconsider the guidelines? *Thorax* **2006;**61:779–782.
15. Direcção Geral de Saúde. Norma nº 018/2011 de 28/09/2011. Cuidados respiratórios domiciliários: Prescrição de oxigenoterapia. Available at www.dgs.pt (last accessed August 28, 2012).
16. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. GOLD executive summary. *Am J Respir Crit Care Med* **2007;**176:532–555.
17. Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. *Eur Respir J* **2004;**23:932–946.
18. American Association for Respiratory Care. AARC clinical practice guidelines: Exercise testing for evaluation of hypoxemia and/or desaturation. *Respir Care* **2001;**46:514–522.
19. Morante F, Guell R, Mayos M. Eficacia de la prueba de 5 minutos de marcha en la valoracion de la oxigenoterapia de deambulation. *Arch Bronconeumol* **2005;**41:596–600.
20. Guyatt GH, Pugsley SO, Sullivan PJ, et al. Effect of encouragement on walking test performance. *Thorax* **1984;**39:818–822.
21. Rous MRG. Long-term oxygen therapy: Are we prescribing appropriately? *Int J COPD* **2008;**3:231–237.
22. Wijkstra PJ, Guyatt GH, Ambrosino N, et al. International approaches to the prescription of long-term oxygen therapy. *Eur Respir J* **2001;**18:909–913.
23. Lewis CA, Eaton TE, Fergusson W, et al. Home overnight pulse oximetry in patients with COPD: More than one recording may be needed. *Chest* **2003;**123:1127–1133.
24. Schenkel NS, Burdet L, Muralt B, et al. Oxygen saturation during daily activities in chronic obstructive pulmonary disease. *Eur Respir J* **1996;**9:2584–2589.

25. Sliwiński P, Lagosz M, Górecka D, et al. The adequacy of oxygenation in COPD patients undergoing long-term oxygen therapy assessed by pulse oximetry at home. *Eur Respir J* **1994;**7:274–278.

26. Pilling J, Cutaia M. Ambulatory oximetry monitoring in patients with severe COPD. *Chest* **1999;**116:314–321.

27. Croxton TL, Bailey WC. Long-term oxygen treatment in chronic obstructive pulmonary disease: recommendations for future research—An NHLBI Workshop report. *Am J Respir Crit Care Med* **2006;**174:373–378.

28. Steventon A, Bardsley M, Billings J, et al. Effect of telehealth on use of secondary care and mortality: Findings from the Whole System Demonstrator cluster randomised trial. *BMJ* **2012;**344:e3874.

29. Noel HC, Vogel DC, Redos JJ, et al. Home telehealth reduces healthcare costs. *Telemed J E Health* **2004;**10:170–183.

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5

DISCUSSÃO GERAL E CONCLUSÕES

Capítulo 5

Discussão geral e conclusões

Os objetivos principais do conjunto de estudos que integram esta Tese foram avaliar a prevalência da DPOC em Portugal, o seu impacto na mortalidade, na morbilidade e no risco de dependência, avaliar a expressão da inflamação sistémica e sua eventual modificação após o exercício físico e clarificar o papel da reabilitação respiratória nos benefícios para a saúde dos doentes com DPOC.

Neste capítulo procurou-se responder, de forma sumária, às questões inicialmente colocadas, já discutidas ao longo da apresentação dos artigos incluídos no Capítulo 4. Apresentam-se as principais conclusões e perspetivas de linhas de investigação futura.

- Dado que a DPOC é uma doença com um impacto negativo em todo o mundo, pela mortalidade e morbilidade associadas, qual o valor estimado da prevalência em Portugal?

  Ao contrário dos estudos de prevalência anteriormente realizados em Portugal [132], o valor de 14,2% evidenciado no estudo 1, indica que a DPOC é uma doença comum. Este facto, aliado ao elevado número de casos de subdiagnóstico, alerta para a necessidade de aumentar a sensibilização da população, dos profissionais de saúde e das autoridades de saúde para esta doença. A maior disponibilização de recursos diagnósticos, nomeadamente do acesso à espirometria, possibilitará o diagnóstico mais precoce. A adequada alocação de recursos terapêuticos. como por exemplo, a criação de novas unidades de reabilitação respiratória e o aumento da capacidade das já existentes, contribuirão para melhorar a acessibilidade dos doentes a uma intervenção com efeitos benéficos largamente comprovados.

  Admitindo que no território nacional a prevalência da DPOC possa não ser uniforme, e que os dados obtidos na região de Lisboa possam não refletir o que se passa nas outras regiões, é importante estender este estudo ao restante

território nacional. Tendo em conta os recursos limitados do nosso país, a alocação dos recursos de saúde deve ser ajustada às necessidades de cada região. Esse será o objetivo do estudo epidemiológico que irá decorrer em Portugal nos próximos meses.

- Dada a elevada mortalidade em doentes com DPOC avançada que são referenciados para reabilitação respiratória, quais são os fatores preditivos clínicos e funcionais da mortalidade, no período de 3 anos que se segue ao programa de reabilitação respiratória, em doentes seguidos em hospital de dia de insuficientes respiratórios?

  O estudo 2 confirmou a elevada taxa de mortalidade – 36,6% - ao longo dos três anos de seguimento de doentes com DPOC em estádio avançado, após cumprimento de um programa de reabilitação respiratória. A mortalidade um ano após o programa foi igualmente elevada – 17,2%.

  As características clínicas que se associaram à mortalidade, podem ser agrupadas em três categorias:

  1º - Ter insuficiência respiratória e estar sob terapêutica com ventilação não invasiva, reflete a evolução da doença para fases de maior gravidade, o que salienta a necessidade da referenciação para reabilitação respiratória em fases mais precoces da doença. A associação do elevado número de exacerbações com a mortalidade foi já amplamente referenciada em estudos anteriores [140, 193-195]. Importa salientar, mais uma vez, a necessidade de uma abordagem preventiva das exacerbações, que passa pela otimização terapêutica, na qual a reabilitação respiratória tem igualmente um papel essencial [196, 197].

  2º - Quanto às comorbilidades que se associam à DPOC, o cancro do pulmão tem aqui características que ensombram ainda mais o prognóstico. O diagnóstico é muitas vezes tardio, dissimulado pelas manifestações habituais da DPOC nesta fase avançada de doença (dispneia intensa, intolerância para pequenos esforços, astenia, adinamia, atrofia e fraqueza muscular) e dado o reduzido *status performance* do doente, as opções terapêuticas, não são habitualmente gratificantes.

A pesquisa sistemática das comorbilidades que foram encontradas neste estudo, nomeadamente o cancro do pulmão e a fibrilhação auricular e o seu tratamento em tempo útil, poderão influenciar o prognóstico a longo prazo [116].

3º - À semelhança do que ocorreu neste estudo, a reduzida capacidade funcional para o exercício, avaliada pela distância na prova de seis minutos de marcha, tem sido interpretada na literatura científica, como um fator prognóstico negativo [198, 199]. O aspeto relevante neste achado está no facto deste fator ser potencialmente modificável, através do treino de exercício [38], o que sublinha o papel da reabilitação respiratória no prognóstico dos doentes com DPOC, mesmo em fase avançada da doença. Após a realização deste estudo, a investigação prosseguiu no sentido de avaliar a associação entre a variação na distância percorrida na prova de marcha de 6 minutos com a RR e a mortalidade 4 anos após o programa [200]. Verificou-se que os doentes que aumentavam pelo menos 25 metros na distância da prova de marcha após a RR, apresentavam menor mortalidade (p=0,047), o que confirma o efeito positivo da RR no prognóstico da doença [200].

- Dada a perda progressiva da capacidade que os doentes com DPOC apresentam na realização das atividades físicas da vida diária, quais os fatores que melhor permitem identificar o risco destes doentes se tornarem dependentes?

  O estudo 3 mostrou que a aplicação de um questionário dirigido às atividades da vida diária permitiu identificar um marcador clínico do risco de dependência. As atividades diárias pesquisadas incluíram as instrumentais como fazer compras ou a lida da casa, os autocuidados como lavar-se, vestir-se ou alimentar-se e os exercícios de locomoção como andar em casa, na rua ou subir escadas.

  A identificação dos sinais precoces de risco de dependência dos doentes com DPOC, como demorar mais tempo, referir dificuldade, ter que fazer pausas ou diminuir a frequência destas atividades, permitiu quantificar este risco através de uma pontuação. No presente estudo, a pontuação encontrada apresentou uma boa correlação com o questionário de avaliação do estado geral de saúde (CAT), complementou a avaliação da capacidade funcional para o exercício com a prova

de marcha de seis minutos e associou-se a outros marcadores clínicos de mau prognóstico, como as exacerbações.

- Sendo a inflamação sistémica um dos fatores que se associa ao aparecimento das manifestações extrapulmonares da DPOC, como a perda de peso, a disfunção do músculo esquelético, a depressão ou a osteoporose e a um pior prognóstico, com maior número de exacerbações e maior mortalidade, qual é a expressão da inflamação avaliada em repouso e a sua eventual modificação após o exercício físico? Quais são as características dos doentes que se associam a essa expressão inflamatória?

  O estudo 4 mostrou uma associação positiva entre a obesidade (índice de massa corporal maior ou igual a 30 $Kg.m^{-2}$) e a expressão inflamatória de todos os genes estudados (interferon gama, interleucina 1beta, interleucina 6, interleucina 8, fator de necrose tumoral alfa, fator de crescimento transformador beta1 e oxido nítrico sintase indutível), bem como uma associação inversa com a desnutrição (índice de massa corporal inferior a 20 $Kg.m^{-2}$) e a expressão inflamatória dos genes IL1b, IL6, TNFa, TGFb e iNOS.

  Não sendo a inflamação sistémica um fenómeno universal em todos os doentes com DPOC, a inflamação persistente constitui contudo, um fator de mau prognóstico, pelo que é importante identificar as caraterísticas dos doentes que podem estar associadas. Estes resultados sugerem um papel importante dos desvios nutricionais na patogénese da inflamação em doentes com DPOC.

  Sabendo a importância do papel da reabilitação respiratória com treino de exercício, aliado à intervenção nutricional, na melhoria da condição física dos doentes com DPOC, com aumento da força e da massa muscular, melhoria da qualidade de vida e do prognóstico a longo prazo, justifica-se a continuidade desta linha de investigação em estudos futuros pesquisando a ligação da inflamação ao exercício e à composição corporal.

- A nova classificação GOLD nas categorias A, B, C e D evidencia melhor a complexidade e a heterogeneidade dos doentes com DPOC. Dado que os componentes agora adicionados à avaliação da obstrução brônquica, nomeadamente os sintomas, o estado geral de saúde e a ocorrência das exacerbações, são potencialmente modificáveis com os programas de RR, quais os resultados na capacidade para o exercício, no controlo da dispneia e no estado geral de saúde, nas diferentes categorias?

  O estudo 5 mostrou melhoria significativa da capacidade de exercício avaliada pela prova de marcha e pela prova de *endurance* e do estado geral de saúde em todas as categorias da DPOC. No impacto da dispneia avaliado pelo índice de Mahler e na prova de marcha, a melhoria mais evidente verificou-se nas categorias A e C, refletindo o facto de serem categorias com menor incapacidade atribuída aos sintomas. A proporção de doentes que obtiveram melhoria clínica significativa foi contudo semelhante em todas as categorias.

  A presença de comorbilidades como as cardiovasculares, a malnutrição ou a obesidade e/ou de complicações como a insuficiência respiratória poderão ter justificado neste estudo, a referenciação para RR de doentes das categorias A e B. Os resultados do programa de RR neste estudo não foram afetados pelo efeito cumulativo das comorbilidades ou das complicações identificadas.

  Concluímos que a referenciação para RR deve ser efetuada valorizando os sintomas, as limitações nas atividades diárias e a perda de qualidade de vida, independentemente da classificação GOLD em A, B, C ou D.

- Sabendo que as comorbilidades são responsáveis pelo agravamento dos sintomas, da qualidade de vida e da capacidade funcional em doentes com DPOC, aumentando o risco de hospitalizações e de mortalidade, qual é a prevalência das comorbilidades na população de doentes que são referenciados para RR e qual é a sua influência nos resultados dos programas?

  O estudo 6 evidenciou uma elevada prevalência de comorbilidades no grupo de doentes que é referenciado para RR, sendo as mais frequentes, as cardiovasculares, as respiratórias e as psicológicas. O número de comorbilidades

não afetou os resultados dos programas de RR, mas algumas, como a insuficiência respiratória e a doença coronária associaram-se a um menor benefício na qualidade de vida, enquanto a síndrome ansiedade/depressão se associou a uma redução menos significativa da dispneia. A identificação e o tratamento sistemático das comorbilidades conferem maior segurança clínica a esta intervenção terapêutica a qual, por apresentar bons resultados, não deve condicionar a referenciação dos doentes.

- Sabendo que a intensidade de treino recomendada para que se obtenham benefícios fisiológicos em doentes com DPOC é entre 60 e 80% da potência aeróbica máxima, qual é a intensidade ótima de treino para que se obtenham os melhores resultados centrados no doente – melhoria da capacidade de exercício, dos sintomas e da qualidade de vida?

  O estudo 7 mostrou melhoria significativa em todos os resultados centrados no doente para ambas as intensidades de treino aeróbio. Entre o grupo de doentes que treinou a 60% da potência aeróbica máxima (Wmax) e o que treinou a 80%, não se verificaram diferenças significativas na melhoria do estado geral de saúde, nos sintomas ou na capacidade para o exercício. Este estudo questiona a indicação sistemática de elevadas intensidades de treino em doentes com DPOC para a obtenção de benefícios a curto prazo. Estudos posteriores poderão avaliar se existem diferenças nos efeitos a longo prazo da aplicação destas intensidades de treino.

- Sabendo que os níveis de atividade física diária nos doentes com DPOC podem ser influenciados por múltiplos fatores e que, por sua vez, a sua diminuição se associa à ocorrência de exacerbações e a maior mortalidade, quais são os principais fatores que influenciam a atividade física na vida diária dos doentes com DPOC? Serão esses fatores potencialmente modificáveis?

  O estudo 8 confirmou que os doentes do sexo masculino com DPOC são marcadamente sedentários, desde uma média diária de cerca de 6000 passos nos doentes com obstrução moderada até apenas 3000 passos diários nos doentes

com obstrução muito grave. Os principais fatores que se associaram ao sedentarismo nestes doentes foram a dispneia e a distância percorrida na prova de marcha de seis minutos. Este estudo sublinha a importância do controlo sintomático da doença, nomeadamente da dispneia, bem como, mais uma vez, o potencial papel da reabilitação respiratória no aumento da capacidade funcional para o exercício e na aquisição de hábitos de vida fisicamente ativa.

- Sabendo que existe perda dos benefícios obtidos nos programas de RR com treino de exercício, caso os doentes não mantenham atividade física regular, qual a evolução da capacidade funcional e do estado de saúde dos doentes com DPOC e insuficiência respiratória crónica, dois anos após completarem um programa de RR?

  O estudo 9 corroborou que apenas os doentes que adotaram comportamentos de atividade física regular após o programa de RR, preservaram ao fim de dois anos, os benefícios inicialmente obtidos. Fica comprovado que os efeitos a curto prazo após o programa de RR e a longo prazo com a manutenção da atividade física regular são alcançados, mesmo em doentes graves com insuficiência respiratória crónica.

- Pressupondo que a atividade física é o fator que melhor prevê a mortalidade global em doentes com DPOC, que esta pode ser avaliada de forma mais rigorosa com o recurso a acelerómetros e cujo incremento pode modificar o prognóstico dos doentes com DPOC, inclusivamente nos insuficientes respiratórios graves cumpridores da oxigenoterapia, conceptualizou-se o sistema TelemOLD.

  Qual é o valor clínico deste sistema de telemonitorização que combina a oximetria e a quantificação da atividade física, na capacidade em detetar dessaturação de oxigénio, em melhor adequar a oxigenoterapia de longa duração e em monitorizar a atividade física regular em doentes com DPOC?

O estudo TelemOLD provou o conceito de que o seu uso pode promover uma melhor adequação da prescrição de OLD, não apenas suspendendo esta terapêutica em doentes que dela não necessitam, com consequentes benefícios económicos e sociais, mas adequando a oxigenoterapia às necessidades individuais reais dos doentes. A análise de custo-benefício feita posteriormente a este estudo, veio confirmar que este sistema tem um potencial valor na relação custo-efetividade.

Outra vantagem deste sistema de telemonitorização é a possibilidade de, após os programas de RR, existir uma maior adesão ao exercício físico e à atividade física regular suportadas por uma monitorização à distância, com reforço de incentivo personalizado. A redução das deslocações ao hospital por reforço da autoeficácia validado pelo sistema à distância e a adequação das estratégias de atividade física em ambiente próprio natural, traduzem-se em ganhos de saúde individuais, com redução dos custos globais associados aos cuidados de saúde.

Como reflexão final importa referir que apesar de ter obtido resposta às interrogações que constituíram os desafios na minha prática clínica e de investigação e que motivaram a realização dos estudos que integram esta Tese, novas interrogações se colocaram no seu desenrolar, pelo que antevejo prosseguir na procura de respostas aos novos desafios.

Bibliografia

1. Make BJ. Pulmonary rehabilitation: myth or reality? Clin Chest Med 1986;7(4):519-540.
2. McArdle WD. Raízes e perspetivas históricas. In: McArdle WD, Katch FI, Katch VL, editors. Fisiologia do Exercício: Nutrição, energia e desempenho humano 7ª edição. Rio de Janeiro: Guanabara Koogan 2011:xxi-ixv.
3. Denison C. Exercise and Food for Pulmonary Invalids. Denver: The Chain & Hardy Co; 1895.
4. Barach AL. A New Type of Oxygen Chamber. J Clin Invest 1926;2(6):463-476.
5. Barach AL, Eckman M. The effects of inhalation of helium mixed with oxygen on the mechanics of respiration. J Clin Invest 1936;2(6):463-476.
6. Barach AL. Ambulatory oxygen therapy: oxygen inhalation at home and out-of-doors. Dis Chest 1959;35(3):229-241.
7. Barach AL, Bickerman HA, Beck G. Advances in the treatment of non-tuberculous pulmonary disease. Bull N Y Acad Med 1952;28(6):353-384.
8. Casaburi R. A brief history of pulmonary rehabilitation. Respir Care 2008;53(9):1185-1189.
9. Petty TL, Nett LM, Finigan MM, Brink GA, Corsello PR. A comprehensive care program for chronic airway obstruction. Methods and preliminary evaluation of symptomatic and functional improvement. Ann Intern Med 1969;70(6):1109-1120.
10. Hodgkin JE, Zorn EG, Connors GL. Pulmonary Rehabilitation: Definition and Essential Components. Butterworth Pub; 1984.
11. ATS. Pulmonary rehabilitation. Am Rev Respir Dis 1981;124(5):663-666.
12. Zuwallack R. A history of pulmonary rehabilitation: back to the future. Pneumonol Alergol Pol 2009;77(3):298-301.
13. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 1984;85(6):751-758.
14. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis 1991;143(1):9-18.
15. Donner CF, Howard P. Pulmonary rehabilitation in chronic obstructive pulmonary disease (COPD) with recommendations for its use. Report of the European Respiratory Society Rehabilitation and Chronic Care Scientific Group (S.E.P.C.R. Rehabilitation Working Group). Eur Respir J 1992(5):266-275.
16. Reardon J, Awad E, Normandin E, Vale F, Clark B, ZuWallack RL. The effect of comprehensive outpatient pulmonary rehabilitation on dyspnea. Chest 1994;105(4):1046-1052.
17. Goldstein RS, Gort EH, Stubbing D, Avendano MA, Guyatt GH. Randomised controlled trial of respiratory rehabilitation. Lancet 1994;344(8934):1394-1397.
18. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Intern Med 1995;122(11):823-832.
19. Maltais F, LeBlanc P, Simard C, Jobin J, Berube C, Bruneau J, et al. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996;154(2 Pt 1):442-447.

20. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet 2000;355(9201):362-368.
21. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. Thorax 2001;56(10):779-784.
22. Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Elkin SL, Garrod R, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults. Thorax 2013;68 Suppl 2:ii1-30.
23. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013;188(8):e13-64.
24. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. Chest 2007;131(5 Suppl):4S-42S.
25. AARC. AARC Clinical Practice Guideline - Pulmonary Rehabilitation. Respir Care 2002;37(5):617-625.
26. GOLD. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2008. Disponível em: http://www.goldcopd.org. Consultado a 12 setembro de 2015.
27. Rodrigues C, Martins V, Munhá J, Aguiar Branco C. Estado da Reabilitação Respiratória em Portugal. Comunicação oral. XXXI Congresso da Sociedade Portuguesa de Pneumologia, Algarve 2015.
28. Yohannes AM, Connolly MJ. Pulmonary rehabilitation programmes in the UK: a national representative survey. Clin Rehabil 2004;18(4):444-449.
29. Walsh JR, McKeough ZJ, Morris NR, Paratz JD. Performance-based criteria are used in participant selection for pulmonary rehabilitation programs. Aust Health Rev 2013;37(3):331-336.
30. Wadell K, Janaudis Ferreira T, Arne M, Lisspers K, Stallberg B, Emtner M. Hospital-based pulmonary rehabilitation in patients with COPD in Sweden--a national survey. Respir Med 2013;107(8):1195-1200.
31. Machaqueiro S. A reabilitação respiratória para doentes com doença pulmonar obstrutiva crónica. Dissertação para Tese de Mestrado em Gestão de Saúde, Julho de 2012. Escola Nacional de Saúde Pública. Universidade Nova de Lisboa.
32. Kruis AL, Chavannes NH. Potential benefits of integrated COPD management in primary care. Monaldi Arch Chest Dis 2010;73(3):130-134.
33. Barbara C, Ramos F, Almeida M, Marques Gomes MJ, Segorbe Luís A. Programa Nacional de Prevenção e Controlo da Doença Pulmonar Obstrutiva Crónica. Direção-Geral da Saúde, Lisboa, 2005.
34. DGS. Orientações Técnicas sobre Reabilitação Respiratória na Doença Pulmonar Obstrutiva Crónica. Circular informativa nº 40A/DSPCD da Direção-Geral da Saúde, 27/10/2009.
35. Simão P, Almeida P. Reabilitação Respiratória. Uma estratégia para a sua implementação. Rev Port Pneumol 2009;3(15):S93-S118.
36. Puhan MA, Gimeno-Santos E, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2011(10):CD005305.
37. DGS. Cuidados Respiratórios Domiciliários: Prescrição de Oxigenoterapia. In: Saúde D-Gd editor Secondary Title|. Vol. Volume|. Place Published|: Publisher|, Year|:Pages|.

38. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2015;2:CD003793.
39. Dogra S, Kuk JL, Baker J, Jamnik V. Exercise is associated with improved asthma control in adults. Eur Respir J 2011;37(2):318-323.
40. Carson KV, Chandratilleke MG, Picot J, Brinn MP, Esterman AJ, Smith BJ. Physical training for asthma. Cochrane Database Syst Rev 2013;9:CD001116.
41. Chalmers JD, Aliberti S, Blasi F. Management of bronchiectasis in adults. Eur Respir J 2015;45(5):1446-1462.
42. Rand S, Hill L, Prasad SA. Physiotherapy in cystic fibrosis: optimising techniques to improve outcomes. Paediatr Respir Rev 2013;14(4):263-269.
43. Spruit MA, Janssen DJ, Franssen FM, Wouters EF. Rehabilitation and palliative care in lung fibrosis. Respirology 2009;14(6):781-787.
44. Ferreira A, Garvey C, Connors GL, Hilling L, Rigler J, Farrell S, et al. Pulmonary rehabilitation in interstitial lung disease: benefits and predictors of response. Chest 2009;135(2):442-447.
45. Martinez-Llorens J, Ramirez M, Colomina MJ, Bago J, Molina A, Caceres E, et al. Muscle dysfunction and exercise limitation in adolescent idiopathic scoliosis. Eur Respir J 2010;36(2):393-400.
46. Salhi B, Troosters T, Behaegel M, Joos G, Derom E. Effects of pulmonary rehabilitation in patients with restrictive lung diseases. Chest 2010;137(2):273-279.
47. Soares Branco P, Barata S, Barbosa J, Cantista M, Lima A, Maia J. Reabilitação Respiratória. Porto: Medesign - Edições e Design de Comunicação, Lda.; 2012.
48. Cruz C, Garcia S. Fisioterapia em doentes com cancro do pulmão em estádio avançado. Revista GECP 2011(2):9-13.
49. Bobbio A, Chetta A, Ampollini L, Primomo GL, Internullo E, Carbognani P, et al. Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. Eur J Cardiothorac Surg 2008;33(1):95-98.
50. Watson T, Mock V. Exercise as an intervention for cancer-related fatigue. Phys Ther 2004;84(8):736-743.
51. Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K. Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer. Cochrane Database Syst Rev 2013;7:CD009955.
52. Garutti Martinez I, Gonzalez Aragoneses F, Ramirez JM. Multimodal rehabilitation program in thoracic surgery. Arch Bronconeumol 2015;51(4):159-160.
53. Makhabah DN, Martino F, Ambrosino N. Peri-operative physiotherapy. Multidiscip Respir Med 2013;8(1):4.
54. Langer D. Rehabilitation in Patients before and after Lung Transplantation. Respiration 2015;89(5):353-362.
55. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation 2006;114(14):1482-1489.
56. Troosters T, Hornikx M, Demeyer H, Camillo CA, Janssens W. Pulmonary rehabilitation: timing, location, and duration. Clin Chest Med 2014;35(2):303-311.
57. Corhay JL, Dang DN, Van Cauwenberge H, Louis R. Pulmonary rehabilitation and COPD: providing patients a good environment for optimizing therapy. Int J Chron Obstruct Pulmon Dis 2014;9:27-39.
58. Sharma S, Arneja A, Talavera F, Salcido R, Kishner S, Massagli T. Pulmonary Rehabilitation. Medscape 2014, disponível em emedicinemedscapecom/article/319885-overview, consultado em 2 outubro 2015.

59. Zanotti E, Felicetti G, Maini M, Fracchia C. Peripheral muscle strength training in bed-bound patients with COPD receiving mechanical ventilation: effect of electrical stimulation. Chest 2003;124(1):292-296.
60. Ngaage DL, Hasney K, Cowen ME. The functional impact of an individualized, graded, outpatient pulmonary rehabilitation in end-stage chronic obstructive pulmonary disease. Heart Lung 2004;33(6):381-389.
61. Franchi M. EFA book on COPD in Europe. European Federation of Allergy and Airways Disease, Brussels, 2011. Disponível em www.efanet.org.
62. Huppmann P, Sczepanski B, Boensch M, Winterkamp S, Schonheit-Kenn U, Neurohr C, et al. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. Eur Respir J 2012;42(2):444-453.
63. Zanaboni P, Lien LA, Hjalmarsen A, Wootton R. Long-term telerehabilitation of COPD patients in their homes: interim results from a pilot study in Northern Norway. J Telemed Telecare 2013;19(7):425-429.
64. Tabak M, Vollenbroek-Hutten MM, van der Valk PD, van der Palen J, Hermens HJ. A telerehabilitation intervention for patients with Chronic Obstructive Pulmonary Disease: a randomized controlled pilot trial. Clin Rehabil 2013;28(6):582-591.
65. Stickland M, Jourdain T, Wong EY, Rodgers WM, Jendzjowsky NG, Macdonald GF. Using Telehealth technology to deliver pulmonary rehabilitation in chronic obstructive pulmonary disease patients. Can Respir J 2011;18(4):216-220.
66. Maltais F, Bourbeau J, Shapiro S, Lacasse Y, Perrault H, Baltzan M, et al. Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2008;149(12):869-878.
67. Guell Rous MR, Diez Betoret JL, Sanchis Aldas J. [Pulmonary rehabilitation and respiratory physiotherapy: time to push ahead]. Arch Bronconeumol 2008;44(1):35-40.
68. Mendes de Oliveira JC, Studart Leitao Filho FS, Malosa Sampaio LM, Negrinho de Oliveira AC, Hirata RP, Costa D, et al. Outpatient vs. home-based pulmonary rehabilitation in COPD: a randomized controlled trial. Multidiscip Respir Med 2010;5(6):401-408.
69. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med 2008;36(8):2238-2243.
70. Bailey P, Thomsen GE, Spuhler VJ, Blair R, Jewkes J, Bezdjian L, et al. Early activity is feasible and safe in respiratory failure patients. Crit Care Med 2007;35(1):139-145.
71. GOLD. Global Initiative for Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of COPD. Revised 2011. Disponível em http://www.goldcopd.org. Consultado em 12 setembro 2015.
72. Hill NS. Pulmonary rehabilitation. Proc Am Thorac Soc 2006;3(1):66-74.
73. Langer D, Hendriks E, Burtin C, Probst V, van der Schans C, Paterson W, et al. A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. Clin Rehabil 2009;23(5):445-462.
74. Langer D, Charususin N, Jacome C, Hoffman M, McConnell A, Decramer M, et al. Efficacy of a Novel Method for Inspiratory Muscle Training in People With Chronic Obstructive Pulmonary Disease. Phys Ther 2015;95(9):1264-1273.
75. Crisafulli E, Costi S, De Blasio F, Biscione G, Americi F, Penza S, et al. Effects of a walking aid in COPD patients receiving oxygen therapy. Chest 2007;131(4):1068-1074.
76. Breyer MK, Breyer-Kohansal R, Funk GC, Dornhofer N, Spruit MA, Wouters EF, et al. Nordic walking improves daily physical activities in COPD: a randomised controlled trial. Respir Res 2010;11:112.
77. Osadnik CR, McDonald CF, Jones AP, Holland AE. Airway clearance techniques for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012;3:CD008328.

78. Effing T, Monninkhof EM, van der Valk PD, van der Palen J, van Herwaarden CL, Partidge MR, et al. Self-management education for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2007(4):CD002990.
79. Spruit MA, Pitta F, McAuley E, ZuWallack RL, Nici L. Pulmonary Rehabilitation and Physical Activity in Patients with COPD. Am J Respir Crit Care Med 2015.
80. Grodner S, Prewitt LM, Jaworsk BA, Myers R, Kaplan RM, Ries AL. The impact of social support in pulmonary rehabilitation of patients with chronic obstructive pulmonary disease. Ann Behav Med 1996;18(3):139-145.
81. Marques A, Jacome C, Cruz J, Gabriel R, Brooks D, Figueiredo D. Family-based psychosocial support and education as part of pulmonary rehabilitation in COPD: a randomized controlled trial. Chest 2015;147(3):662-672.
82. Rodrigues F. [Limiting factors of exercise capacity in patients with COPD]. Rev Port Pneumol 2004;10(1):9-61.
83. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164(5):770-777.
84. Barreiro E, Bustamante V, Cejudo P, Galdiz JB, Gea J, de Lucas P, et al. Guidelines for the Evaluation and Treatment of Muscle Dysfunction in Patients With Chronic Obstructive Pulmonary Disease. Arch Bronconeumol 2015;51(8):384-395.
85. O'Donnell DE. Breathlessness in patients with chronic airflow limitation. Mechanisms and management. Chest 1994;106(3):904-912.
86. Van Vliet M, Spruit MA, Verleden G, Kasran A, Van Herck E, Pitta F, et al. Hypogonadism, quadriceps weakness, and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;172(9):1105-1111.
87. Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RS, Cooper CB. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997;155(5):1541-1551.
88. McArdle WD. Treinamento para potência anaeróbica e aeróbica. In: McArdle WD, Katch FI, Katch VL, editors. Fisiologia do Exercício: Nutrição, energia e desempenho humano 7ª edição. Rio de Janeiro: Guanabara Koogan 2011:459-505.
89. Vogiatzis I, Terzis G, Stratakos G, Cherouveim E, Athanasopoulos D, Spetsioti S, et al. Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. Chest 2011;140(3):744-752.
90. Almagro P, Lopez Garcia F, Cabrera F, Montero L, Morchon D, Diez J, et al. Comorbidity and gender-related differences in patients hospitalized for COPD. The ECCO study. Respir Med 2010;104(2):253-259.
91. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43(7):1334-1359.
92. Probst VS, Troosters T, Pitta F, Decramer M, Gosselink R. Cardiopulmonary stress during exercise training in patients with COPD. Eur Respir J 2006;27(6):1110-1118.
93. Puhan MA, Busching G, Schunemann HJ, VanOort E, Zaugg C, Frey M. Interval versus continuous high-intensity exercise in chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2006;145(11):816-825.
94. Belman MJ. Exercise in patients with chronic obstructive pulmonary disease. Thorax 1993;48(9):936-946.
95. Vogiatzis I, Terzis G, Nanas S, Stratakos G, Simoes DC, Georgiadou O, et al. Skeletal muscle adaptations to interval training in patients with advanced COPD. Chest 2005;128(6):3838-3845.

96. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med 1996;153(3):976-980.
97. Marquis K, Debigare R, Lacasse Y, LeBlanc P, Jobin J, Carrier G, et al. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166(6):809-813.
98. Bernard S, Whittom F, Leblanc P, Jobin J, Belleau R, Berube C, et al. Aerobic and strength training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159(3):896-901.
99. Ortega F, Toral J, Cejudo P, Villagomez R, Sanchez H, Castillo J, et al. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166(5):669-674.
100. Velloso M, Jardim JR. Functionality of patients with chronic obstructive pulmonary disease: energy conservation techniques. J Bras Pneumol 2006;32(6):580-586.
101. Mkacher W, Mekki M, Tabka Z, Trabelsi Y. Effect of 6 Months of Balance Training During Pulmonary Rehabilitation in Patients With COPD. J Cardiopulm Rehabil Prev 2015;35(3):207-213.
102. Riebe D. General principles of exercise prescription. Chapter 7. In: Pescatello LS, Arena R, Riebe D, Thompson PD, editors. ACSM's Guidelines for Exercise Testing and Prescription, 9th edition. Baltimore: Wolters Kluwer, Lippincott Williams & Wilkins, 2014.
103. Sillen MJ, Franssen FM, Vaes AW, Delbressine JM, Wouters EF, Spruit MA. Metabolic load during strength training or NMES in individuals with COPD: results from the DICES trial. BMC Pulm Med 2014;14:146.
104. Almeida P, Rodrigues F. Exercise training modalities and strategies to improve exercise performance in patients with respiratory disease. Rev Port Pneumol 2014;20(1):36-41.
105. Pitta F, Troosters T, Probst VS, Langer D, Decramer M, Gosselink R. Are patients with COPD more active after pulmonary rehabilitation? Chest 2008;134(2):273-280.
106. O'Donnell DE, McGuire M, Samis L, Webb KA. The impact of exercise reconditioning on breathlessness in severe chronic airflow limitation. Am J Respir Crit Care Med 1995;152(6 Pt 1):2005-2013.
107. Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW. Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. Eur Respir J 1998;12(2):363-369.
108. Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am J Med 2000;109(3):207-212.
109. Guyatt GH, King DR, Feeny DH, Stubbing D, Goldstein RS. Generic and specific measurement of health-related quality of life in a clinical trial of respiratory rehabilitation. J Clin Epidemiol 1999;52(3):187-192.
110. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002;19(3):398-404.
111. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987;42(10):773-778.
112. Finnerty JP, Keeping I, Bullough I, Jones J. The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease: a randomized controlled trial. Chest 2001;119(6):1705-1710.
113. Puhan MA, Scharplatz M, Troosters T, Steurer J. Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality -- a systematic review. Respir Res 2005;6:54.

114. Sabit R, Griffiths TL, Watkins AJ, Evans W, Bolton CE, Shale DJ, et al. Predictors of poor attendance at an outpatient pulmonary rehabilitation programme. Respir Med 2008;102(6):819-824.
115. Wilson K, Brookfield D. Effect of goal setting on motivation and adherence in a six-week exercise programme. International Journal of Sports and Exercise Physiology 2009(6):89-100.
116. GOLD. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2015. Disponível em: http://www.goldcopd.org. Consultado a 12 setembro de 2015.
117. Anderson D, Macnee W. Targeted treatment in COPD: a multi-system approach for a multi-system disease. Int J Chron Obstruct Pulmon Dis 2009;4:321-335.
118. Rodrigues F. Role of extra-pulmonary factors - depression, muscle weakness, health-related quality of life - in COPD evolution. Rev Port Pneumol 2010;16(5):709-715.
119. Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. Clinicoecon Outcomes Res 2013;5:235-245.
120. Lamprecht B, Soriano JB, Studnicka M, Kaiser B, Vanfleteren L, Gnatiuc L, et al. Determinants of Underdiagnosis of COPD in national and international surveys. Chest 2015;2015/05/08(2292636 [pii]10.1378/chest.14-2535).
121. Burney P, Jithoo A, Kato B, Janson C, Mannino D, Nizankowska-Mogilnicka E, et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty--a BOLD analysis. Thorax 2014;69(5):465-473.
122. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J 2006;28(3):523-532.
123. Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, et al. COPD in Japan: the Nippon COPD Epidemiology study. Respirology 2004;9(4):458-465.
124. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007;370(9589):741-750.
125. Menezes AM, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, Valdivia G, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet 2005;366(9500):1875-1881.
126. Schirnhofer L, Lamprecht B, Vollmer WM, Allison MJ, Studnicka M, Jensen RL, et al. COPD prevalence in Salzburg, Austria: results from the Burden of Obstructive Lung Disease (BOLD) Study. Chest 2007;131(1):29-36.
127. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. MMWR Surveill Summ 2002;51(6):1-16.
128. Ford ES, Mannino DM, Wheaton AG, Presley-Cantrell L, Liu Y, Giles WH, et al. Trends in the use, sociodemographic correlates, and undertreatment of prescription medications for chronic obstructive pulmonary disease among adults with chronic obstructive pulmonary disease in the United States from 1999 to 2010. PLoS One 2014;9(4):e95305.
129. Miravitlles M, Soriano JB, Garcia-Rio F, Munoz L, Duran-Tauleria E, Sanchez G, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. Thorax 2009;64(10):863-868.
130. Reis Ferreira JM, Matos MJ, Rodrigues F, Belo A, Brites H, Cardoso J, et al. Prevalence of bronchial obstruction in a tobacco smoke exposed population - the PNEUMOBIL project. Rev Port Pneumol 2009;15(5):803-846.
131. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis 1978;118(6 Pt 2):1-120.

132. Cardoso J, Ferreira JR, Almeida J, Santos JM, Rodrigues F, Matos MJ, et al. Chronic obstructive pulmonary disease in Portugal: Pneumobil (1995) and 2002 prevalence studies revisited. Rev Port Pneumol 2013;19(3):88-95.
133. Buist AS, Vollmer WM, Sullivan SD, Weiss KB, Lee TA, Menezes AM, et al. The Burden of Obstructive Lung Disease Initiative (BOLD): rationale and design. COPD 2005;2(2):277-283.
134. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997;349(9064):1498-1504.
135. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3(11):e442.
136. WHO. World Health Statistics 2008. Part 1. Ten highlights in health statistics. Available from http:/www.who.int/gho/publications.
137. Hoyert DL, Xu J. Deaths: preliminary data for 2011. Natl Vital Stat Rep 2012;61(6):1-51.
138. European Lung White Book, European Respiratory Society 2013. Disponível em http://www.erswhitebook.org/files/public/Chapters/13_COPD.pdf, consultado em 1 de setembro de 2015.
139. Ford ES. Trends in Mortality From COPD Among Adults in the United States. Chest 2015;148(4):962-970.
140. Anzueto A. Impact of exacerbations on COPD. Eur Respir Rev 2010;19(116):113-118.
141. Hoogendoorn M, Hoogenveen RT, Rutten-van Molken MP, Vestbo J, Feenstra TL. Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. Eur Respir J 2011;37(3):508-515.
142. Cavailles A, Brinchault-Rabin G, Dixmier A, Goupil F, Gut-Gobert C, Marchand-Adam S, et al. Comorbidities of COPD. Eur Respir Rev 2013;22(130):454-475.
143. Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL. Variables related to increased mortality following out-patient pulmonary rehabilitation. Eur Respir J 1996;9(3):431-435.
144. Piquet J, Chavaillon JM, David P, Martin F, Blanchon F, Roche N. High-risk patients following hospitalisation for an acute exacerbation of COPD. Eur Respir J 2013;42(4):946-955.
145. Singanayagam A, Schembri S, Chalmers JD. Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. Ann Am Thorac Soc 2013;10(2):81-89.
146. Garcia-Aymerich J, Gomez FP, Benet M, Farrero E, Basagana X, Gayete A, et al. Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes. Thorax 2011;66(5):430-437.
147. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006;27(2):397-412.
148. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009;33(5):1165-1185.
149. Garcia-Rio F, Miravitlles M, Soriano JB, Munoz L, Duran-Tauleria E, Sanchez G, et al. Systemic inflammation in chronic obstructive pulmonary disease: a population-based study. Respir Res;11:63.
150. Agusti AG. Systemic effects of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005;2(4):367-370; discussion 371-362.
151. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 2004;59(7):574-580.
152. Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS One;7(5):e37483.

153. van der Vlist J, Janssen TW. The potential anti-inflammatory effect of exercise in chronic obstructive pulmonary disease. Respiration;79(2):160-174.
154. Van Helvoort HA, Heijdra YF, Thijs HM, Vina J, Wanten GJ, Dekhuijzen PN. Exercise-induced systemic effects in muscle-wasted patients with COPD. Med Sci Sports Exerc 2006;38(9):1543-1552.
155. van Helvoort HA, van de Pol MH, Heijdra YF, Dekhuijzen PN. Systemic inflammatory response to exhaustive exercise in patients with chronic obstructive pulmonary disease. Respir Med 2005;99(12):1555-1567.
156. Rabinovich RA, Figueras M, Ardite E, Carbo N, Troosters T, Filella X, et al. Increased tumour necrosis factor-alpha plasma levels during moderate-intensity exercise in COPD patients. Eur Respir J 2003;21(5):789-794.
157. Koechlin C, Maltais F, Saey D, Michaud A, LeBlanc P, Hayot M, et al. Hypoxaemia enhances peripheral muscle oxidative stress in chronic obstructive pulmonary disease. Thorax 2005;60(10):834-841.
158. Swallow EB, Reyes D, Hopkinson NS, Man WD, Porcher R, Cetti EJ, et al. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. Thorax 2007;62(2):115-120.
159. Barreiro E, Schols AM, Polkey MI, Galdiz JB, Gosker HR, Swallow EB, et al. Cytokine profile in quadriceps muscles of patients with severe COPD. Thorax 2008;63(2):100-107.
160. Canavan J, Linton-Willoughby B, Garrod R. Acute Exercise Testing of COPD Patients: The Effect on Systemic Inflammatory Proteins. Current Respiratory Medicine Reviews 2011;7:464-474.
161. Crul T, Spruit MA, Gayan-Ramirez G, Quarck R, Gosselink R, Troosters T, et al. Markers of inflammation and disuse in vastus lateralis of chronic obstructive pulmonary disease patients. Eur J Clin Invest 2007;37(11):897-904.
162. Bruunsgaard H. Physical activity and modulation of systemic low-level inflammation. J Leukoc Biol 2005;78(4):819-835.
163. Petersen AM, Pedersen BK. The role of IL-6 in mediating the anti-inflammatory effects of exercise. J Physiol Pharmacol 2006;57 Suppl 10:43-51.
164. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 2006;173(12):1390-1413.
165. van Wetering CR, Hoogendoorn M, Mol SJ, Rutten-van Molken MP, Schols AM. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. Thorax 2010;65(1):7-13.
166. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res 2010;11:122.
167. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnzeel PL, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187(7):728-735.
168. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;186(2):155-161.
169. Rodrigues F, Grafino M, Papoila A, Faria I, Pontes da Mata J, Felix F. Cardiopulmonary exercise test in preoperative assessment of lung resection surgery. Oral communication in 12th European Practicum on Clinical Exercise Testing, Porto 2008.
170. Areias V, Carreira S, Anciaes M, Pinto P, Barbara C. Co-morbidities in patients with gold stage 4 chronic obstructive pulmonary disease. Rev Port Pneumol 2014;20(1):5-11.
171. Vanfleteren LE. Does COPD stand for "COmorbidity with Pulmonary Disease"? Eur Respir J 2015;45(1):14-17.

172. Datta D, ZuWallack R. High versus low intensity exercise training in pulmonary rehabilitation: is more better? Chron Respir Dis 2004;1(3):143-149.
173. Gosselink R, Troosters T, Decramer M. Exercise training in COPD patients: the basic questions. Eur Respir J 1997;10(12):2884-2891.
174. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;172(1):19-38.
175. Kesaniemi YK, Danforth E, Jr., Jensen MD, Kopelman PG, Lefebvre P, Reeder BA. Dose-response issues concerning physical activity and health: an evidence-based symposium. Med Sci Sports Exerc 2001;33(6 Suppl):S351-358.
176. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012;380(9838):219-229.
177. Cristi-Montero C, Rodriguez FR. [The paradox of being physically active but sedentary or sedentary but physically active]. Rev Med Chil 2014;142(1):72-78.
178. Healy GN, Wijndaele K, Dunstan DW, Shaw JE, Salmon J, Zimmet PZ, et al. Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Diabetes Care 2008;31(2):369-371.
179. Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, et al. Breaks in sedentary time: beneficial associations with metabolic risk. Diabetes Care 2008;31(4):661-666.
180. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. Eur Respir J 2009;33(2):262-272.
181. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;171(9):972-977.
182. Burtin C, Decramer M, Gosselink R, Janssens W, Troosters T. Rehabilitation and acute exacerbations. Eur Respir J 2011;38(3):702-712.
183. Waschki B, Kirsten A, Holz O, Muller KC, Meyer T, Watz H, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. Chest 2011;140(2):331-342.
184. Guell R, Casan P, Belda J, Sangenis M, Morante F, Guyatt GH, et al. Long-term effects of outpatient rehabilitation of COPD: A randomized trial. Chest 2000;117(4):976-983.
185. Soicher JE, Mayo NE, Gauvin L, Hanley JA, Bernard S, Maltais F, et al. Trajectories of endurance activity following pulmonary rehabilitation in COPD patients. Eur Respir J 2012;39(2):272-278.
186. Gimeno-Santos E, Frei A, Steurer-Stey C, de Batlle J, Rabinovich RA, Raste Y, et al. Determinants and outcomes of physical activity in patients with COPD: a systematic review. Thorax 2014;69(8):731-739.
187. Danilack VA, Weston NA, Richardson CR, Mori DL, Moy ML. Reasons persons with COPD do not walk and relationship with daily step count. COPD 2014;11(3):290-299.
188. Petty TL, Bliss PL. Ambulatory oxygen therapy, exercise, and survival with advanced chronic obstructive pulmonary disease (the Nocturnal Oxygen Therapy Trial revisited). Respir Care 2000;45(2):204-211; discussion 211-203.
189. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet 1981;1(8222):681-686.
190. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 1980;93(3):391-398.
191. Zamith M, Marques Gomes MJ. Novas tecnologias da informação em Pneumologia. Rev Port Pneumol 2005;XI(3 [Supl 1]):S21-S28.

192. Zamith M, Cardoso T, Matias I, Marques Gomes MJ. Home telemonitoring of severe chronic respiratory insufficient and asthmatic patients. Rev Port Pneumol 2009;15(3):385-417.
193. Seemungal TA, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. Int J Chron Obstruct Pulmon Dis 2009;4:203-223.
194. Almagro P, Calbo E, Ochoa de Echaguen A, Barreiro B, Quintana S, Heredia JL, et al. Mortality after hospitalization for COPD. Chest 2002;121(5):1441-1448.
195. Quintana JM, Esteban C, Unzurrunzaga A, Garcia-Gutierrez S, Gonzalez N, Barrio I, et al. Predictive score for mortality in patients with COPD exacerbations attending hospital emergency departments. BMC Med 2014;12:66.
196. Seymour JM, Moore L, Jolley CJ, Ward K, Creasey J, Steier JS, et al. Outpatient pulmonary rehabilitation following acute exacerbations of COPD. Thorax 2010;65(5):423-428.
197. Kon SS, Canavan JL, Man WD. Pulmonary rehabilitation and acute exacerbations of COPD. Expert Rev Respir Med 2012;6(5):523-531; quiz 531.
198. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). Eur Respir J 2008;31(4):869-873.
199. Spruit MA, Polkey MI, Celli B, Edwards LD, Watkins ML, Pinto-Plata V, et al. Predicting outcomes from 6-minute walk distance in chronic obstructive pulmonary disease. J Am Med Dir Assoc 2012;13(3):291-297.
200. Guerreiro C, Madama D, Rodrigues F. Functional capacity variation after Pulmonary Rehabilitation in COPD patients – a survival predictor? Oral communication, ERS Annual Congress, Amsterdam 2015.